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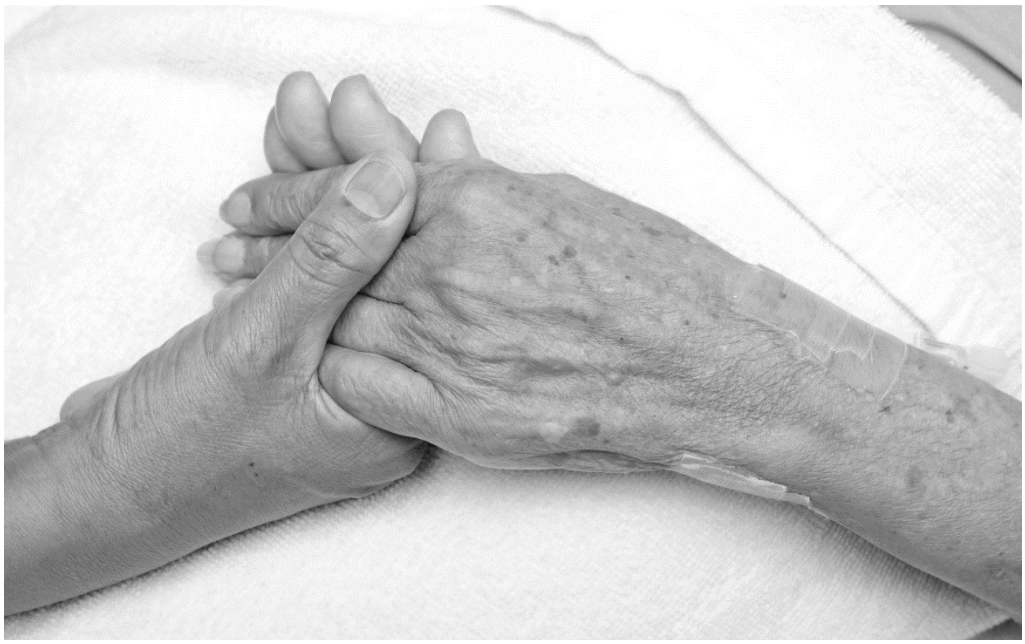
FACULTY OF HEALTH AND MEDICAL SIENCES

Symptoms and problems reported by cancer patients admitted to specialized palliative care



PhD Thesis

Maiken Bang Hansen

This thesis has been submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen 12 April 2019

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Preface

When cancer patients are admitted to specialized palliative care, they suffer from advanced disease and are often troubled by severe symptoms and problems, and they, as well as their families, need help. The quality of life of the patients (and their families) is extremely important in this very last phase of life and therefore working with quality improvement in specialized palliative care in my professional life since 2012 and in the past years working on this PhD-thesis has been a very meaningful journey for me.

I would like to give a great thanks to my supervisor professor Mogens Grønvold for your high professionalism, for inspiring discussions, for your always positive and creative mind but at the same time your thoroughness, for believing in me and always being supportive. Your great commitment to quality of life research in palliative care is inspiring and I have enjoyed working with you in the past seven years.

I would also like to thank my other supervisors, PhD and senior researcher Lone Ross Nylandsted and statistician Morten Aagaard Petersen for your great support during my PhD, your great expertise, your forthcomingness and endless willingness to discuss clinical aspects, statistical problems etc. Also, a great thanks to my co-authors; Mathilde Adsersen and Leslye Rojas for great discussions and valuable cooperation in drafting of the papers.

I am also grateful to all my current and former colleges at the Research Unit, Department of Palliative Medicine, for making everyday life working with this PhD-thesis great both professionally and socially. Also, a great thanks to my 'office-mates' Mathilde Adsersen, Tina Harmer Lassen and Leslye Rojas for endless support and great talks.

I would like to thank all SPC units making this project possible by delivering data to the Danish Palliative Care Database with a high completeness and quality and also a thanks to the Danish Cancer Society and University of Copenhagen for funding this PhD-thesis.

Lastly, a very special thanks to my lovely family and my friends for always listening to me, helping me and being supportive.

Original papers

This thesis is based upon the following four papers:

1. Hansen MB, Petersen MA, Ross L, Groenvold M. Should analyses of large, national palliative care data sets with PRO be restricted to units with high patient participation? (*Under review*)
2. Hansen MB, Ross L, Petersen MA, Groenvold M. Age, cancer site and gender associations with symptoms and problems in specialised palliative care: a large, nationwide, register-based study. BMJ Support Palliat Care. 2019 Sep 28. pii: bmjspcare-2019-001880. doi: 10.1136/bmjspcare-2019-001880. PubMed PMID: 31563863. (*Published*)
3. Hansen MB, Ross L, Petersen MA, Adsersen M, Rojas-Concha L, Groenvold M. Patients referred to specialized palliative care by general practitioners and hospital units reported similar levels of symptoms - a nationwide study of 31,139 Danish cancer patients. (*Submitted*)
4. Hansen MB, Petersen MA, Ross L, Adsersen M, Rojas-Concha L, Groenvold M. Information on symptoms and problems improved survival predictions in 28,681 cancer patients at the start of specialized palliative care - a nationwide register based study. (*Under review*)

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Introduction

Background

Palliative care

The World Health Organization (WHO) defines palliative care as '*an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual*'. Thus, the focus of palliative care is to improve the quality of life (QOL) of patients with life-threatening illness and their families by preventing and relieving physical, psychosocial and spiritual problems [1]. This definition is adopted in many countries worldwide, including Denmark. Palliative care can be divided into specialized palliative care (SPC) and general/basic palliative care. In specialized palliative care, providing palliative care is the main function of the provided service, whereas in general/basic palliative care, providing palliative care is only a part of the provided service [2, 3]. This PhD thesis concerns specialized palliative care, i.e., hospice and palliative care units in hospitals.

Specialized palliative care as we know it today started in UK where the first modern hospice, St Christopher's Hospice, opened in London in 1967. The hospice was founded by Dame Cicely Saunders and the focus of the hospice was clinical care of patients as well as research and education [4]. Great advances in end-of-life care were made at St Christopher's hospice in terms of improved symptom control and by broadening the scope of end-of-life care with the introduction of the concept of 'total pain' including not only physical but also emotional, social and spiritual pain [5]. Cicely Sanders and her endeavor on improving the quality of life of patients at the end of life served as an inspiration to the hospice and palliative care movement spreading worldwide [4]. Inspired by Cicely Saunders, the first hospice outside UK opened in the US in 1974 and a few years later palliative care services opened in other countries in Western Europe and continued to spread worldwide during the next decades [4, 6, 7]. The first Danish hospice opened in 1992 and today there are 44 SPC units in Denmark [8].

Quality development in palliative care

Since the early 1980s, palliative care has been gradually acknowledged worldwide and has gained more political attention. Several national as well as international organizations have been founded to increase the availability and quality of palliative care e.g. the National Hospice Organization (today renamed the National Hospice and Palliative Care Organization) in the US in 1978 and the European Association for Palliative Care (EAPC) in 1988 [2, 4, 7, 9-11].

Several international reports have been made to promote and increase the quality of palliative care. In 2003, a report from the Council of Europe, gave several guidelines for palliative care. European countries were encouraged to cooperate, to make national plans for palliative care and to strive to continuously improve the quality of palliative care [3, 4]. To improve the quality of palliative care, some initiatives were urged: development of evidence based clinical guidelines, multidisciplinary audits, research (including cross national research) as a basis for best palliative care practice, education in palliative care and development of national and/or local quality indicators [3].

More recent reports from powerful international organizations including WHO, the Worldwide Palliative Care Alliance (WPCA) and EAPC all aimed at improving the availability and quality of palliative care and enable better integration of palliative care across health services [2, 9, 12, 13].

In Denmark, the political interest in palliative care increased in the 1980s and in 1985 the Danish Health Authority published their first report with recommendations on how to improve palliative care; these recommendations have been updated several times since [2, 14, 15]. Later, in 2011, the Danish Health Authority recommended that palliative care should be offered to all patients with life threatening disease [16]. Several Danish organizations have been established and have worked to improve the availability and quality of palliative care in Denmark and in 2009 the first Danish Knowledge Centre for Palliative Care (PAVI) was formed following suggestions from five palliative care organizations. In the same year, the Danish Multidisciplinary Cancer Group for Palliation (DMCG-PAL) and the Danish Palliative Care Database (DPD) were established with financial support from the Ministry of Health [2]. Since 2009, PAVI has mapped SPC in Denmark. DMCG-PAL has aimed at improving the quality of SPC by publishing several national clinical guidelines and by making curriculums for different professions in palliative care. DPD has defined, monitored and reported national quality indicators [17, 18].

Symptom assessment tools in palliative care

To obtain high quality in palliative care it is of course critical to meet the primary aim of palliative care, i.e., to prevent and relieve problems in patients with life threatening illness [1, 4]. To obtain

this goal, symptom assessment is crucial [1, 19]. Therefore, to be able to assess symptoms comprehensively with minimal patient burden, Bruera and colleges developed the Edmonton Symptom Assessment System (ESAS) in 1987 in their palliative clinic. ESAS was simple to complete and patients could assess ten symptoms in less than five minutes [20]. Since, other studies have documented the importance of patient reported symptoms (as opposed to assessments by health care professionals) and the importance of using systematic tools for symptom assessment, in order to comprehensively detect the patients' symptoms [21-23]. Today, ESAS has been validated extensively and is one of the most widely used symptom assessment tools in palliative care. Other tools have been developed and validated in palliative care as well and are also used widely today, e.g., the European Organisation for Research and Treatment of Cancer Quality of Life Questionaire-Core-15-Palliative Care questionnaire (EORTC QLQ-C15-PAL), the Palliative care Outcome Scale (POS), POS-S Symptom list and Memorial Symptom Assessment Scale (MSAS) [24].

EORTC QLQ-C15-PAL is a shortened version of EORTC QLQ-C30 adapted to patients in palliative care [25]. EORTC QLQ-C30 is one of the most widely used tools to assess symptoms and problems in cancer patients [26, 27] and has been validated extensively [28-33] and has also been used for cancer patients in palliative care [34-37]. The EORTC QLQ-C15-PAL was developed to obtain a short version of EORTC QLQ-C30 suitable for patients in palliative care. This was done by shortening the multi-item scales of EORTC QLQ-C30 where possible and by omitting items/scales from EORTC QLQ-C30, which were not highly relevant or even inappropriate in palliative care [25]. When EORTC QLQ-C15-PAL was developed it was criticized for not including measures of existential and spiritual issues and worries related to the future and relatives, and even to need further validation [38]. Th developers of the EORTC QLQ-C15-PAL did, however, aim at shortening the EORTC QLQ-C30 questionnaire and therefore, as the initial step, did not aim at generating new items or scales which could (also) be relevant in palliative care. Instead, they suggested to supplement EORTC QLQ-C15-PAL with additional items when it is considered to be important [39]. Later, EORTC QLQ-C15-PAL has been validated further [40-45]. Recently, a systematic review has evaluated the psychometric quality of self-reported instruments assessing health related QOL of advanced cancer patients for use in palliative care [46]. When the quality of 39 identified instruments were evaluated, EORTC QLQ-C15-PAL together with one other instrument (EORTC QLQ-BM22) were deemed to have the highest psychometric quality. EORTC QLQ-BM22 is a module for patients with bone metastases and should be used together with EORTC QLQ-C30 and thus is more extensive for patients to answer

than EORTC QLQ-C15-PAL. Thus, in the review EORTC QLQ-C15-PAL is suggested to be an adequate instrument to use when measuring health related QOL in advanced cancer patients [46].

Research in SPC using patient reported symptoms and problems

To alleviate symptoms and problems of patients admitted to SPC, the health care professionals of course need to be aware of the patients' symptoms/problems. To obtain a comprehensive symptom assessment in patients admitted to SPC it is important that the symptom assessment is done by the patients themselves with the use of a symptom assessment tool, since health care professionals often fail to detect all symptoms in this phase [21-23, 47].

In addition to the important clinical use of systematic patient reported symptoms in SPC, the systematic reporting of symptoms can also be used in research to understand the symptomatology of patients in SPC at a specific point in time (e.g. the start of SPC) and how the patients' symptomatology evolves over time in SPC, how symptoms cluster, or how other factors or interventions in SPC can affect the symptomatology of the patients. Such research can range from small studies including only patients from a single SPC unit to national (or international) studies on a population level.

To be able to obtain a better understanding of the symptomatology of patients at the start of SPC at a population level more research from large studies including patients across different kinds of SPC units is needed. Such studies could possibly add knowledge of the symptomatology of patients admitted to SPC by investigating e.g. the prevalence and level of symptoms and problems at the start of SPC and by elucidating how different factors (e.g., sociodemographic factors, clinical factors and survival time) are associated with the symptomatology.

Are symptom/problem-scores reported by patients in SPC representative?

Clearly, patient reported outcomes can only be obtained from patients capable of reporting their symptoms/problems. Since patients admitted to SPC are severely ill and close to death, it is not feasible for all patients to report their symptoms/problems. That is, the most severely ill patients with shortest survival time will likely be under-represented in research of symptomatology in specialized palliative care [35]. Since the most ill patients with very short survival are unlikely to report their symptoms/problems the average level and frequency of reported symptoms/problems will probably be lower than if all patients admitted to SPC had reported their symptoms/problems. Acknowledging that some patients are not capable of reporting their symptoms/problems, it is nevertheless crucial to obtain symptom/problem reporting from as representative a sample as

possible of patients capable at reporting their symptoms/problems if research is to give an understanding of the symptomatology of all cancer patients at the start of SPC.

The annual report from the Danish Palliative Care Database shows different response rates to the EORTC QLQ-C15-PAL questionnaire across Danish SPC units [8]. One could suspect that in SPC units with low response rates, reporting of symptoms/problems were only obtained from the most well patients, i.e., those where symptom/problem reporting were easiest to obtain. No previous study has, however, investigated if symptom-problem scores from SPC units with low response rates (compared to those with higher) are likely to be biased, i.e., to underestimate the level of symptomatology. With the increasing interest in analyzing large, national data sets with patient reported outcomes (PROs) in palliative care it is important to know if units with low response rates should be excluded in data analyses in order to prevent the possible effects of selection bias.

Symptoms and problems in SPC and their association with clinical and demographic factors

Previous studies have described the symptomatology of cancer patients referred to SPC, and as expected they all found that patients were severely affected by symptoms and problems. The prevalence and severity of the symptoms varied extensively across the studies and explanations for this may include differences in study populations due to differences in criteria for admitting patients to SPC between countries, regions and types of SPC units (i.e., hospice, palliative care teams in hospitals or home based palliative care teams), differences in how the symptoms/problems were assessed, different cut off values used to decide when a symptom was present, etc. [36, 48-65].

Other studies investigated the associations between clinical and demographic factors, respectively, and symptoms/problems. These studies found inconsistent results concerning the associations between gender, age, and cancer diagnosis, respectively, and symptoms/problems among patients at the start of SPC [36, 48, 49, 51, 52, 56, 65, 66]. Concerning the association between gender and symptoms/problems a few studies found an increased level and risk of nausea [36, 49, 52, 65] as well as an increased risk of early satiety in women compared to men [49, 52, 65], but the association between gender and other symptoms/problems were inconsistent across the studies [36, 49, 52, 65]. Previous studies on the association between age and the risk of symptoms and problems were inconsistent [36, 48, 52, 65]; relatively consistent findings were a reduced risk of depression [48, 52, 65] and pain [36, 52, 65] with increased age.

Significant associations between cancer site and symptom risk or symptom level for some symptoms were found in three studies on patients admitted to SPC [51, 56, 65], whereas one study

found no effect of cancer site [36]. The inconsistent findings across studies of the association between symptoms/problems and gender, age and cancer diagnosis, respectively, may be explained in the same way as above, i.e., by differences in patient populations and methods to assess symptoms/problems, but possibly also by differences in how age and cancer diagnoses were categorized and how the association between symptoms/problems and gender, age and cancer diagnosis, respectively, were analyzed across studies.

Most of the previous studies on the prevalence and level of symptoms/problems in patients admitted to SPC as well as the studies on the association between symptoms/problems and gender, age and cancer diagnoses, respectively, included patients from only a single SPC unit and some did not use validated tools for symptom assessment. Therefore, large studies across different types of SPC units with patient reported symptoms using validated tools would be relevant in order to improve the understanding of the symptomatology at the start of SPC and how it is associated with gender, age and cancer diagnosis, respectively.

Is the level of symptoms and problems at the start of SPC associated with the health care sector (general practitioner versus hospital physician) referring the patients to SPC?

The numbers of SPC beds and SPC teams in Denmark are much lower than recommended by the European Association of Palliative Care [67, 68]. The limited SPC capacity is concerning since SPC is associated with increased quality of life [69, 70].

There may be many different reasons for referral to SPC. One of the frequently emphasized reasons is symptom relief [71-76], but the symptomatology entailing a SPC referral is not clearly defined. In Denmark, patients are referred to SPC by a physician, in most cases this is either a general practitioner (the primary health care sector) or a hospital physician (the secondary health care sector) [8]. Competences, tasks, patient populations, prior patient knowledge etc. do, however, differ across the primary and secondary health care sectors and therefore, the *threshold* for referring a patient to SPC for symptom/problem control may not be the same in the two health care sectors. Therefore, the *threshold* for referring a patient to SPC for symptom/problem control may differ across the two health care sectors; e.g. the physicians in contact with the sickest patients (i.e., the hospital physicians compared to the general practitioners) may perceive higher levels of symptoms as normal or the physicians who most often see patients with high symptom levels may feel more confident in relieving complex symptoms. Confidence in physical symptom management is one of the (sensible) main reasons for non-referral to SPC [71]. Also, the likelihood

for referring patients to SPC is probably higher for physicians with the greatest insight into what SPC can offer and for physicians who believe that SPC deliver high quality work [75-77].

In countries with insufficient SPC capacity it is important that the symptomatology needed for a SPC referral is equal for patients referred by physicians in the primary and secondary health care sector (unless there could be other reasons explaining the differences), ensuring patients with the most complex symptomatology access to SPC across health care sectors. However, due to the many differences between the primary and secondary health care sector one could speculate that this might not be the case. It is therefore important to investigate if the symptomatology is different for patients referred by general practitioners and patients referred by hospital physicians, but to our knowledge this has not previously been done.

Association between symptoms and problems and survival time from start of SPC

Patients referred to SPC are a subgroup of advanced cancer patients, often polysymptomatic [36, 52, 55, 57, 59, 61, 62, 64] and often referred to SPC specifically for symptom relief [71-76]. Previous systematic reviews on advanced cancer patients with short survival time (≤ 3 months expected survival) have found some symptoms and problems to be associated with survival time [78-80]. Inconsistent findings were found across the few studies investigating the association between patient reported symptoms at the time of referral to SPC and survival time [36, 81-83]. However, rather consistently across the studies, problems related to eating (reduced appetite, early satiety and dysphagia) [36, 81-83], poor performance status/poor physical function [36, 82, 83], and poor cognitive function [36, 81] were found to be associated with reduced survival time, although the strength of the associations varied across the studies. The inconsistent findings across the studies in whether and how strongly different symptoms were associated with survival time, might be explained by differences in study populations due to different criteria for admitting patients to SPC across countries and types of SPC units (hospice, palliative care teams in hospitals etc.) as well as differences in how symptoms were assessed and how they were analyzed across studies. Thus, it is uncertain if and how symptoms and problems are associated with survival time in patients referred to SPC. However, if symptoms/problems in patients referred to SPC are associated with survival time they may help predict survival time at the start of SPC.

Some tools including symptoms/problems as well as other variables have been developed to predict survival time in advanced cancer patients (the Palliative Prognostic Index, the Palliative Prognostic Score, etc.) [78, 81, 84-93]. The symptom/problem measures included in the tools were, however, often not self-reported, some tools were not validated and finally, even though the

symptoms/problems were associated with survival time, it was not tested whether the survival prediction actually improved by including the symptoms/problems [78, 81, 84-93].
Therefore, it is important to conduct large studies across different types of SPC units to investigate how patient reported symptoms at the start of SPC are associated with survival time and if information on symptoms can improve survival predictions at the start of SPC.

Research questions and aims

The overall aim of this PhD thesis was to investigate the symptomatology of cancer patients at the start of SPC and its association with different variables. The specific research questions were:

- Is response rate to EORTC QLQ-C15-PAL associated with the level of symptoms and problems in cancer patients at the start of SPC? (Paper 1)
- What is the level and prevalence of symptoms/problems of cancer patients at the start of SPC and is the level of symptoms/problems associated with gender, age and cancer diagnosis? (Paper 2)
- Is referral sector (general practitioner vs. hospital physician) associated with the level and number of symptoms/problems at SPC referral and does the association between referral sector and symptoms/problems vary with the type of SPC the patients are referred to (outpatient or inpatient)? (Paper 3)
- Is the level of symptoms and problems at the start of SPC associated with survival time and does information on symptoms/problems improve survival prediction compared to prediction based solely on clinical variables? (Paper 4).

Material and methods

Data sources

This PhD thesis was based on data from the Danish Palliative Care Database (DPD). The DPD includes information on all Danish patients referred to SPC from January 1st, 2010 and forward [18]. The DPD includes clinical and demographic information for all patients referred to SPC, reasons for not admitting patients to SPC, and for admitted patients there are information on type of the first SPC contact (inpatient/outpatient), sociodemographic factors, multidisciplinary conference, and symptoms/problems reported on the European Organisation for Research and

Treatment of Cancer Quality of Life Questionaire-Core-15-Palliative Care questionnaire (EORTC QLQ-C15-PAL) [18].

The EORTC QLQ-C15-PAL questionnaire is a shortened version of the EORTC QLQ-C30, adapted to patients in palliative care to give the minimal patient burden but still preserving the questions important for patients in palliative care [18, 25]. EORTC QLQ-C15-PAL comprises ten scales; six one-item scales (dyspnea, insomnia, appetite loss, constipation, nausea/vomiting and overall quality of life), three two-item scales (pain, fatigue and emotional function) and one three-item scale (physical function) [25].

Study population

The study population in this PhD thesis was adult cancer patients admitted to SPC who reported their symptoms/problems in the EORTC QLQ-C15-PAL questionnaire at the start of SPC (from three days prior to admission to the day of admission to SPC) and who had died (Figure 1). The time-period for SPC admittance and death was 2010-2015 in Paper 1, and because more data was available when Papers 2-4 were made the time-period was expanded to 2010-2017. Some patients were referred (and admitted) to more than one SPC unit. All patient referrals were included in Paper 1 whereas only the first patient referral was included in Papers 2-4 because we only wished to include each patient once when studying the levels of symptoms/problems and their association with gender, age etc. at the start of palliative care (Figure 1). Paper 1 included 24,589 patient admissions of adult cancer patients, with admittance to SPC and death in the period 2010-2015, who had answered the EORTC QLQ-C15-PAL questionnaire at the start of SPC (Figure 1). Paper 2 included 31,771 unique (only first SPC referral) adult cancer patients, admitted to SPC and deceased in the period 2010-2017, who had answered the EORTC QLQ-C15-PAL questionnaire at the start of SPC. Paper 3 included the same patients as in Paper 2, except for those *not* referred to SPC by the general practitioner (GP) or hospital physician, i.e., 31,139 patients. Paper 4 also included the same patients as in Paper 2, except for those admitted to a non-SPC unit with only a visit from the SPC team, i.e., Paper 4 included 28,681 patients admitted to a SPC unit as inpatients or outpatients (Figure 1).

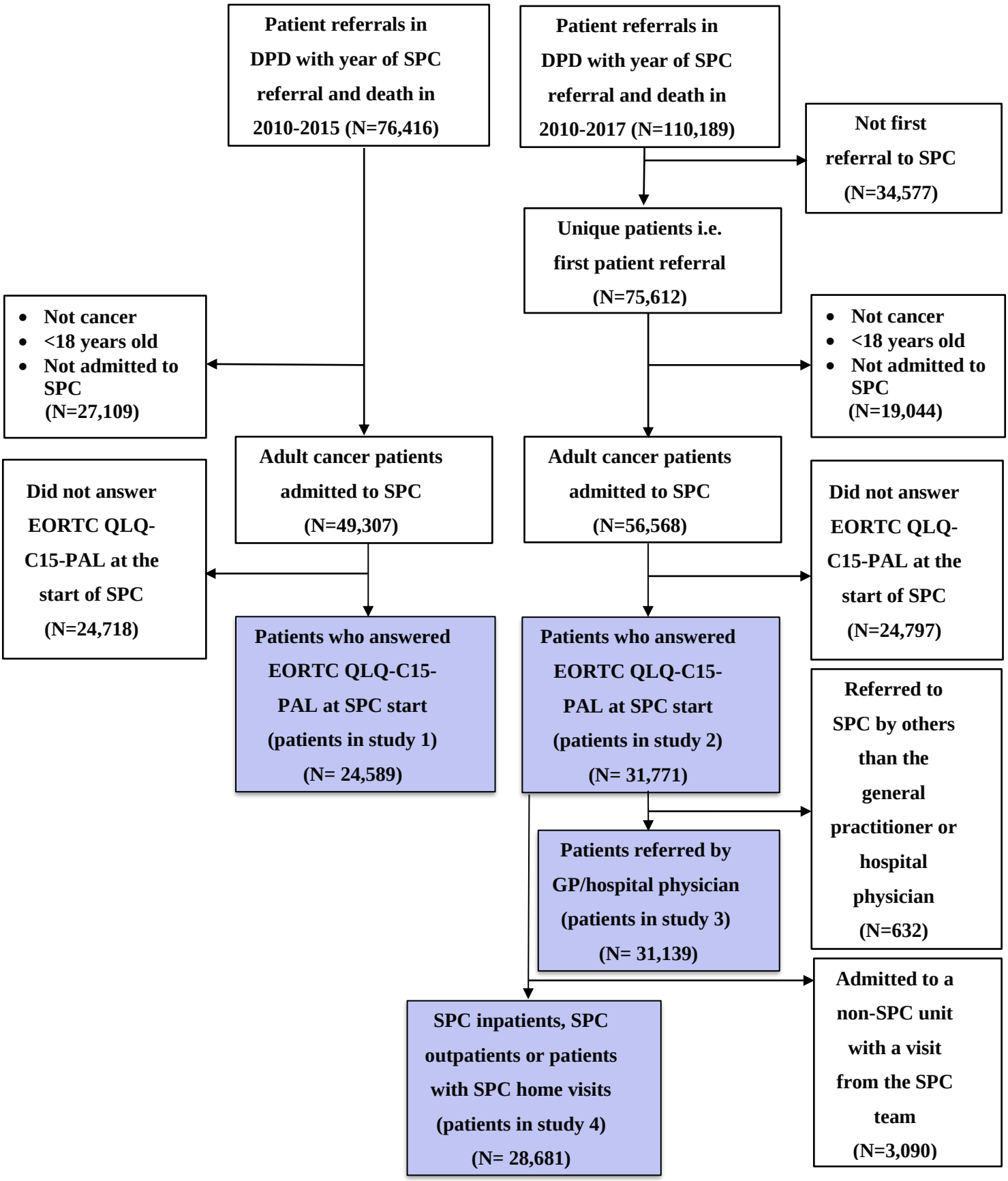

Fig. 1: Flowchart of patients in Papers 1-4. DPD= The Danish Palliative Care Database. SPC=Specialized palliative Care. GP= general practitioner.

Computing of variables

Symptom and problem scores

All questions of the EORTC QLQ-C15-PAL questionnaire, except for overall QOL, are answered using a 4-point response scale: 'not at all', 'a little', 'quite a bit', 'very much'. Overall QOL is reported on a 7-point scale where 1 corresponds to 'very poor' and 7 to 'excellent'. The three items on physical functioning do not have any time frame; all other items refer to the past week [25]. The responses to the EORTC QLQ-C15-PAL were converted into 0-100 scales according to the scoring manual [25, 94]; for the two functional scales and QOL, higher scores represent better functioning/QOL, whereas for the seven symptom scales, higher scores represent worse symptom burden [25, 94].

Response rate

To be able to study how response rate was associated with symptom/problem-scores, response rate to EORTC QLQ-C15-PAL was computed according to SPC unit and year of admission and thereafter allocated to each patient. Thus, if a patient was admitted to a palliative care unit, e.g., palliative care team (PCT) X in 2012, the patient was allocated the response rate of PCT X in 2012. The response rate was grouped into; <20.0%, 20.0-29.9%, 30.0-39.9% 40.0-49.9%, 50.0-59.9% and ≥ 60%

Statistical analyses

Table 1 gives an overview of statistical analyses, variables included in the statistical models (i.e., outcomes, explanatory variables, variables controlled for and random effects) and the number of models in Papers 1-4.

Table 1: Statistical methods, explanatory variables, outcomes, control variables and random effects included in the statistical models as well as the number of models in Papers 1-4

	Paper 1 (N=24,589)	**Paper 2 (N=31,771)**	**Paper 3 (N=31,139)**	**Paper 4 (N=28,681)**
Statistical methods	Linear regression analyses	Ordinal logistic regression analyses	Ordinal logistic regression analyses	a) Cox regression analyses b) Logistic regression analyses
Outcomes	Symptom/ problem scores (continuous)*	Symptom/ problem scores (categorical)	Symptom/problem scores (categorical), number of symptoms/ problems and number of severe symptoms/ problems	a) Survival time from start of SPC (days) b) One-week and one-month survival
Explanatory variables	Response rate to EORTC QLQ-C15-PAL	Gender, age, cancer diagnosis	Referral sector (general practitioner vs. hospital physician)	a) Symptom/ problem scores (continuous)* b) four models**
Variables controlled for	Type of SPC unit (hospice vs. palliative care team)	Gender, age, cancer diagnosis	Gender, age, cancer diagnosis, SPC unit	a) Clinical variables (gender, age, cancer diagnosis, patient type (inpatient vs. outpatient) b) four models**

Random effects	SPC unit and patient ID			
Number of models	One for each symptom/ Problem, i.e. 10 models	One model for each symptom/ problem, i.e. 10 models	One model for each symptom/problem, one for number of symptoms/ problems and one for number of severe symptoms/ problems, i.e. 12 models	a) One model for palliative care teams (PCTs) and one for hospice, i.e. two models b) four models** for one-week and four models for one-month survival for PCTs and hospice, respectively, i.e. 16 models

*** Symptom/problem-scores were treated as continuous variables. **Model 1: Clinical variables and symptoms/problems, Model 2: Only clinical variables, Model 3: Clinical variables and symptoms/problems with highest predictive value, Model 4: Only symptoms/problems with highest predictive value**

Paper 1 (linear regression)

To study the association between response rate and level of the symptoms/problems, multiple linear regression analyses were performed with response rate to the EORTC QLQ-C15-PAL questionnaire as a categorical explanatory variable (with the highest response rate group as reference, i.e. ≥60%) and the level of symptoms/problems as outcome. Thus, ten multiple linear regression analyses were performed, with each of the symptom/problem-scores as outcomes. The analyses were controlled for type of SPC (PCT vs. hospice). Random effects for the specific SPC unit and patient ID, respectively, were included in the models because patients from the same SPC unit were expected to be more similar than patients from different SPC units and because assessments from the same patient were expected to be correlated. Multiple linear regression was chosen instead of ordinal logistic regression because the results (mean differences) are easy to interpret and because ordinal logistic regression was not possible to perform in SAS with random effects included. In Paper 1 it was decided that on the 0-100-point symptom/problem scales, the difference in symptom/problem score for SPC units

with different response rates had to be ≥5 to be considered clinically relevant. This cut point was chosen based on results and conclusions from previous studies [95-99]. In those studies, 10 was, however, often used as the clinically relevant cut point [100], but a more conservative cut point of 5 was chosen in Paper 1 because it was important not to miss relevant differences.

Papers 2-3 (ordinal logistic regression)

To study the associations between gender, age and cancer site, ordinal logistic regression analyses were performed with gender, age and cancer site as explanatory variables (and mutual control variables because they were included in the same model) and the level of each symptom/problem as the outcome, i.e., 10 analyses were performed. In Paper 3, to study the association between referral sector (general practitioner vs. hospital physician) and symptoms/problems, ordinal logistic regression analyses were performed with referral sector as explanatory variable and symptom/problem-level, the number of symptoms/problems and the number of severe symptoms/problems, respectively, as outcome, i.e., in total 12 analyses. All analyses were controlled for the effect of gender, age, cancer site and specific SPC unit. To test if the association between referral sector and symptoms/problems differed when patients were referred to outpatient and inpatient SPC, an interaction term between type of SPC (outpatient or inpatient) and referral sector (general practitioner or hospital physician) was added to the models. If the interaction was insignificant it was removed from the models. In Paper 3, to quantify the magnitude of significant odds ratios, multiple linear regression was performed to obtain the mean differences for these. A mean difference ≥5 points (on a 0-100-point scale) between patients referred by general practitioners and hospital physicians was considered clinically relevant [95-99].

Paper 4 (Cox regression and logistic regression)

In Paper 4, Cox regression analyses were performed to study how clinical variables (gender, age, cancer site, type of patient (inpatient/outpatient)) and symptoms/problems were associated with survival time. Thus, the clinical variables and symptoms/problems were included in the model as explanatory variables and survival time (days) as outcome. Backwards stepwise selection was performed until the model only included explanatory variables significantly associated with survival time, using a significance level of <0.05. A model was made for PCT and hospice, respectively, because hospice patients, compared to PCT patients, were on average closer to death

and therefore it was important to study the association between different variables and survival time in these two 'populations' separately.

Afterwards logistic regression analyses were performed with one-week (and one-month) survival (yes/no) as outcome to obtain the area under the receiver operating characteristic (ROC) curve (AUC) for prediction models with different explanatory variables. Higher AUC levels meant higher precision in classifying patients correctly as surviving one-week (or one-month). AUC for different models were compared to assess whether survival prediction improved when symptoms/problems were included in a model including only clinical variables. The AUC was computed for four different one-week and one-month prediction models, including different explanatory variables:

- Model 1: all significant explanatory variables from the final Cox model
- Model 2: only the clinical variables from the final Cox model
- Model 3: the clinical variables plus a few symptoms/problems where it was possible to retain almost the same AUC level as in model 1 (i.e. the simplest 'symptom/problem enhanced' model)
- Model 4: symptoms/problems from model 3 only.

Results

Study participants in Papers 1-4 compared to non-participants

Table 2 shows demographic and clinical variables for respondents to EORTC QLQ-C15-PAL (i.e., the study population in Papers 2-4) and non-respondents in Papers 2-4 (Table 2). Respondents and non-respondents were similar in their gender distribution, in who referred them to SPC and with regard to age (Table 2). The distribution of cancer diagnoses differed slightly between respondents and non-respondents: patients with brain and CNS cancer, leukaemia and 'unknown cancer site' were slightly underrepresented in the study population. The response rate was markedly lower for inpatients compared to outpatients (45.0% vs. 60.4%) and for hospice patients compared to palliative care team patients (40.0% vs. 61.4%). Respondents survived 27,4 days longer on average compared to non-respondents. Thus, the proportion of inpatients, patients from hospice and those with short survival time were underrepresented in the study population in Papers 2-4. When

respondents and non-respondents in Paper 1 were compared, largely the same differences as just described were seen (data not shown here).

Table 2: Characteristics for those who answered EORTC QLQ-C15-PAL (i.e., the study population) and non-respondents in Papers 2-4*. P-values for comparison of respondents and non-respondents on demographic and clinical variables.

	Answered EORTC QLQ-C15-PAL			
	Yes	**No**	**Response rate**	**P-value**
All	31,771 (100%)	24,797 (100%)	56.2%	
Gender				P<0.001
Women	15,491 (48.8 %)	12,636 (51.0%)	55.1%	
Men	16,280 (51.2%)	12,161 (49.0%)	57.2%	
Age				P<0.001
Mean	69.3	70.2	-	
Median	70	71	-	
Range	18-101	18-105	-	
Cancer site/diagnosis				P<0.001
Head and neck	927 (2.9%)	689 (2.8%)	57.4%	
Esophagus	1,133 (3.6%)	730 (2.9%)	60.8%	
Stomach	947 (3.0%)	692 (2.8%)	57.8%	
Small intestine	228 (0.7%)	141 (0.6)	61.8%	
Colon and rectum	3,900 (12.3%)	2,784 (11.2%)	58.4%	
Liver etc.	1,079 (3.4 %)	934 (3.8%)	53.6%	
Pancreatic	2,420 (7.6%)	1,791 (7.2%)	57.5%	
Lung etc.	8,378 (26.4%)	6,269 (25.3%)	57.2%	
Melanoma	635 (2.0%)	516 (2.1%)	55.2%	
Breast	2,534 (8.0%)	1,958 (7.9%)	56.4%	
Cervical	295 (0.9%)	217 (0.9%)	57.6%	
Endometrial	373 (1.2%)	310 (1.3%)	54.6%	
Ovarian	1,126 (3.5%)	831 (3.4%)	57.5%	
Prostate	2,388 (7.5%)	1,590 (6.4%)	60.0%	
Bladder	797 (2.5%)	696 (2.8%)	53.4%	
Kidney etc.	940 (3.0%)	690 (2.8%)	57.7%	
Brain and CNS	849 (2.7%)	1,170 (4.7%)	42.1%	
Lymphoma	196 (0.6%)	234 (0.9%)	45.6%	
Myelomatosis	273 (0.9%)	237 (1.0%)	53.5%	
Leukaemia	321 (1.0%)	369 (1.5%)	46.5%	
Sarcomas, other soft tissues	357 (1.1%)	251 (1.0%)	58.7%	
Other cancer site	974 (3.1%)	862 (3.5%)	53.1%	
Unknown cancer site	701 (2.2%)	836 (3.4%)	45.6%	

Patient type (inpatient/outpatient)				P<0.001
Outpatient	24,848 (78.2%)	16,317 (65.8%)	60.4%	
Inpatient	6,923 (21.8%)	8,463 (34.1%)	45.0%	
Unknown	0 (0.0%)	17 (0.1%)	0	
Type of SPC				P<0.001
Palliative care team	26,211 (82.5%)	16,465 (66.4%)	61.4%	
Hospice	5,560 (17.5%)	8,332 (33.6%)	40.0%	
Referral unit				P<0.001
General practitioner	7,905 (24.9%)	5,932 (23.9%)	57.1%	
Hospital physician	23,234 (73.1%)	17,997 (72.6%)	56.4%	
Others	632 (2.0%)	868 (3.5%)	42.1%	
Survival time from start of SPC				P<0.001
Mean	108.8	81.4	-	
Median	47	24	-	
Range	0-2452	0-2603	-	

* In Paper 3 those not referred by the general practitioner or physicians in hospitals were excluded (632 of the 31,771 patients) and in Paper 4 patients admitted in a non-SPC unit with only a visit from a SPC team were excluded (3,090 of the 31,771 patients).

Paper 1

The research question in Paper 1 was: *'Is response rate to the EORTC QLQ-C15-PAL questionnaire associated with the level of symptoms and problems in cancer patients at the start of SPC?*'. Figure 2 shows the results from the multiple linear regression analyses, i.e., it shows the mean difference (MD) in symptom/problem-scores between SPC units with the highest response rate of ≥60% (i.e., the reference group) and SPC units with lower response rates (<20%, 20-29%, 30-39%, 40-49%, 50-59%). Response rate was significantly associated with six symptoms/problems: dyspnea, appetite loss, fatigue, nausea, emotional function and physical function, but pairwise comparisons between SPC units with the highest response rate (≥60%) and SPC units with lower response rates, only found small significant differences in mean scores (1.7-5.7 points on a 0-100-point scale) (Figure 2). Except for one difference at 5.7 points (in nausea), i.e., at the borderline of clinically relevance, all the significant differences were <5 points and were thus not clinically relevant.

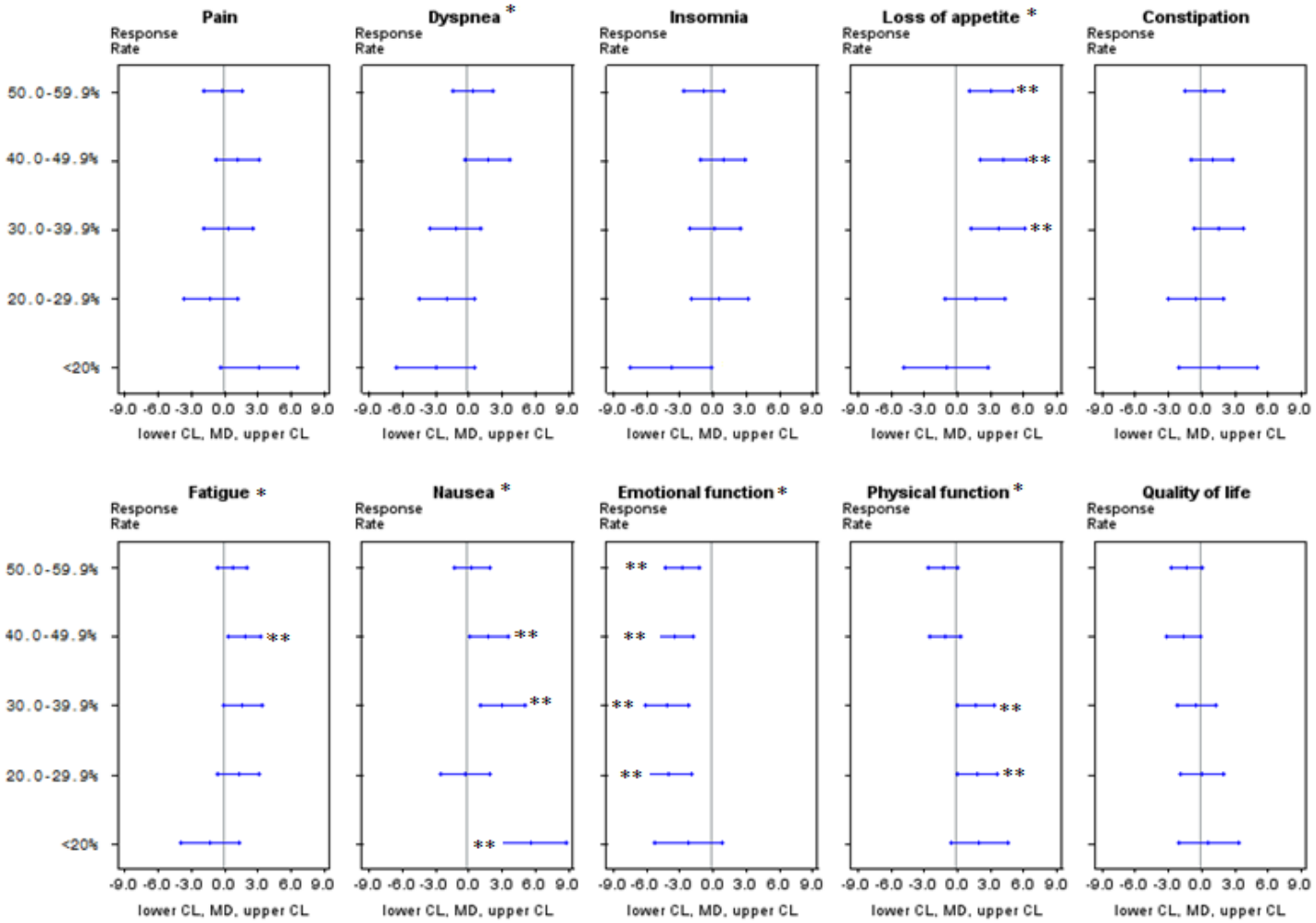

Fig. 2: Association between response rate (≥60.0% is reference) and symptom/problem-scores adjusted for hospice/palliative care team from multiple linear regression analyses with random effect of patient id and SPC unit. CL = confidence limit, MD= mean difference. For the symptom scales, a negative MD means the <60.0% response rate groups have lower symptom scores than the ≥60.0% response rate group. For functional and QOL scales, a positive MD means the <60.0% response rate groups have higher functioning/QOL than the ≥60.0% response rate group. *Overall p-value for the association between response rate and scale score was <0.05. **P-value for difference in symptom score between the ≥60.0% response rate group and one of the lower response rate groups was <0.05.

Paper 2

The first research question in Paper 2 was: *'What is the level and prevalence of symptoms/problems of cancer patients at the start of SPC?'*. Cancer patients in this study reported severe levels of symptom/problems at the start of SPC. The highest mean symptom scores (on a 0-100-point scale) were reported for fatigue (mean=75), appetite loss (mean=57), and pain (mean=55) and the patients experienced low physical function (mean=29) and poor quality of life (mean=40) (Figure 3, top). The frequency of many symptoms/problems was high and more than 3/4 of the patients experienced at least 'a little' fatigue (95%), physical function problems (89%), appetite loss (79%) and pain (77%), respectively (Figure 3, bottom).

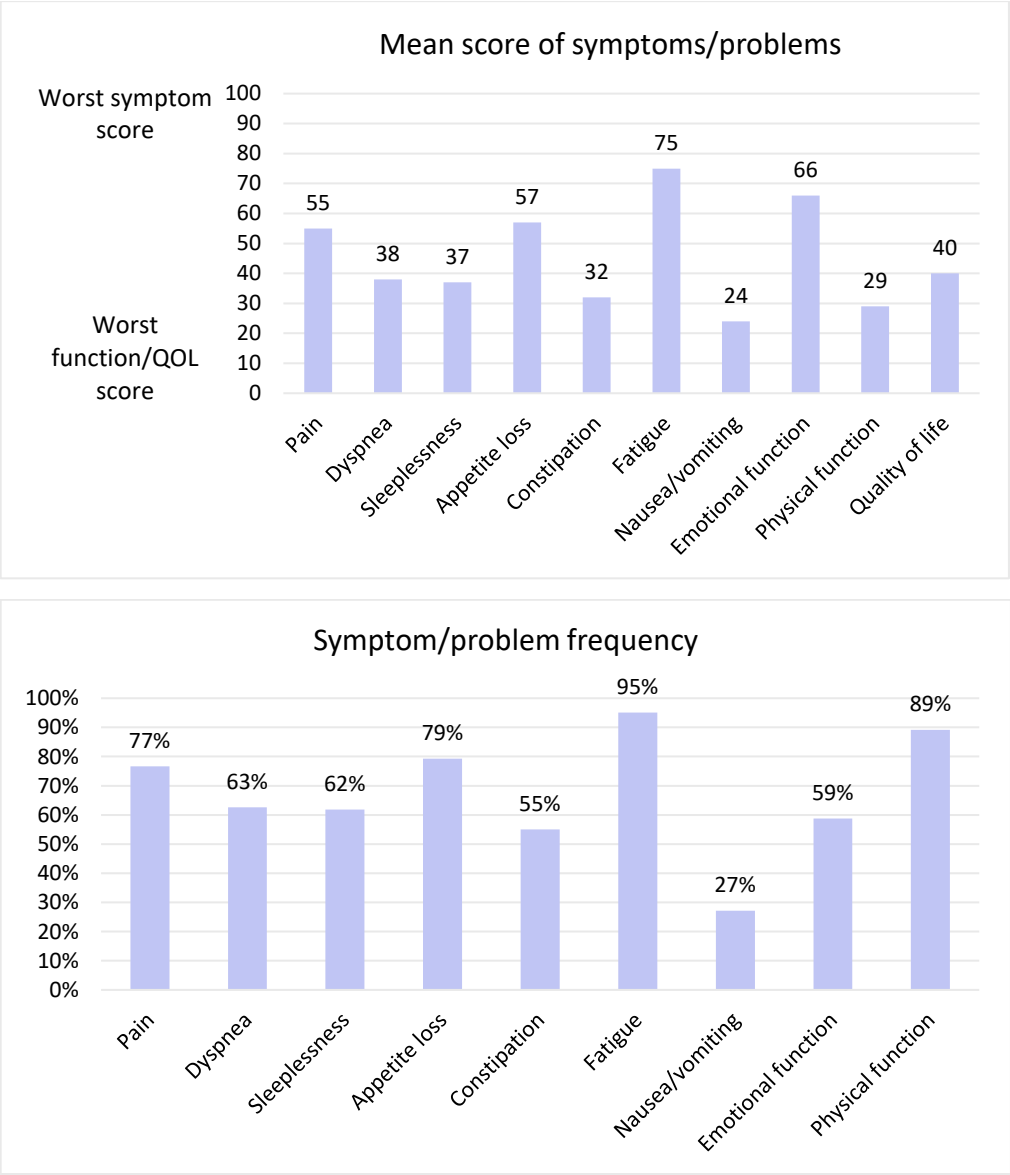

Fig 3: Symptom/problem mean scores and proportion of patients reporting a symptom/problem at least 'a little'.

The second research question of Paper 2 was '*Is the level of symptoms/problems associated with gender, age and cancer diagnosis?'* Gender was significantly associated with all symptoms/problems except for appetite loss, constipation and overall QOL (Table 3). The strongest associations between gender and symptoms/problems were women's higher risk of nausea (OR: 1.40, 95% CI: 1.34;1.47) and lower risk of sleeplessness (OR: 0.81, 95% CI: 0.77;0.85) (Table 3). Age was significantly associated with all symptoms/problems except for dyspnea (Table 3). The strongest associations between age and symptoms/problems were the higher risk of poor physical function (OR: 1.28, 95% CI: 1.26;1.31) and lower risk of pain (OR: 0.81, 95% CI: 0.80;0.83), sleeplessness (OR: 0.79, 95% CI: 0.77;0.80) and poor emotional function (OR=0.85, 95% CI: 0.84;0.87) with increasing age (Table 3).

Table 3: Odds ratios (OR) and 95% CI for the ten symptoms/problems for women vs. men and with a 10-year increase in age from ordinal logistic regression

	Gender		Age	
	OR	95% CI	OR	95% CI
Pain	1.11*	(1.07-1.16)	0.81*	(0.80-0.83)
Dyspnea	0.88*	(0.84-0.93)	1.02	(1.00-1.04)
Sleeplessness	0.81*	(0.77-0.85)	0.79*	(0.77-0.80)
Appetite loss	1.04	(0.99-1.09)	1.12*	(1.10-1.14)
Constipation	0.96	(0.91-1.00)	0.96*	(0.94-0.98)
Fatigue	1.14*	(1.09-1.19)	1.09*	(1.07-1.11)
Nausea/vomiting	1.40*	(1.34-1.47)	0.93*	(0.91-0.95)
Emotional functioning	1.18*	(1.12-1.23)	0.85*	(0.84-0.87)
Physical functioning	1.12*	(1.07-1.17)	1.28*	(1.26-1.31)
Overall QOL	0.99	(0.95-1.04)	0.97*	(0.95-0.98)

***P≤0.05**

In the descriptive (unadjusted) analyses symptom/problem-scores varied substantially according to cancer diagnosis (Table 4). Patients with cancer in the brain and central nervous system (CNS) had the best (lowest) symptom score for six of seven symptoms but on the contrary a poor physical function (Table 4). In the ordinal logistic regression analysis, diagnosis was significantly associated with all symptoms/problems ($p \leq 0.01$) and the descriptive findings were largely supported by the findings in the logistic regression analyses.

Table 4: Mean scores for the ten symptoms/problems for all cancer patients and according to cancer site/diagnosis.

		Cancer site/diagnoses																						
	All	Head/neck	Esophagus	Stomach	Small intestine	Colon/rectum	Liver etc.	Pancreatic	Lung etc.	Melanoma	Breast	Cervical	Endometrial	Ovarian	Prostate	Bladder	Kidney etc.	Brain/CNS	Lymphoma	Myelomatosis	Leukemia	Sarcomas etc.	Other	Unknown
Symptoms (100= worst score)																								
Pain	**55**	59	53	54	57	55	53	58	54	52	55	63	59	52	62	63	60	30	49	61	39	63	56	58
Dyspnea	**38**	34	35	32	30	31	32	28	53	31	38	28	31	39	27	29	37	15	34	32	38	36	35	37
Sleeplessness	**37**	41	39	38	42	37	37	39	39	36	35	42	35	37	34	40	37	29	36	31	37	42	39	38
Appetite loss	**57**	54	66	69	64	60	63	68	54	53	54	56	63	64	54	63	56	25	50	53	59	55	55	62
Constipation	**32**	30	34	36	31	28	30	36	33	33	31	32	35	34	38	39	36	25	25	29	21	34	33	34
Fatigue	**75**	71	73	77	75	75	77	76	75	73	74	75	75	79	72	77	76	70	79	75	78	71	74	78
Nausea/Vomiting	**24**	17	27	35	34	25	28	32	19	27	26	28	31	35	23	28	26	12	16	19	20	19	21	26
Function and QOL (0= worst score)																								
Emotional function	**66**	64	66	67	66	69	68	67	65	67	66	65	65	65	68	65	66	68	69	66	71	66	66	64
Physical function	**29**	38	33	32	29	31	30	35	27	28	29	31	28	29	30	24	26	25	21	25	24	29	29	22
Quality of life	**40**	40	40	40	42	41	40	40	40	42	41	42	38	38	41	35	40	42	42	40	40	39	38	36

Symptoms: Higher scores represent worse symptoms. Function/QOL: Lower scores represent worse function/QOL. For each of the ten symptoms/problems: Red cells = the diagnosis with the highest symptom/lowest function mean scores, green cells= the diagnosis with the lowest symptom-/highest function- mean scores.

Paper 3

The first research question in Paper 3 was *'Is referral sector (general practitioner vs. hospital physician) associated with the level and number of symptoms/problems at SPC referral?'*. The differences in symptom/problem-scores between patients referred to SPC by the general practitioner (GP) and by the hospital physician were all less than 5 points (on a 0-100-point scale) and the difference in the mean number of symptoms/problems and severe symptoms/problems for the two different referring sectors were 0.1-0.2 (Figure 4).

In the ordinal logistic regression analyses, patients referred by GPs compared to patients referred by hospital physicians had an increased risk of pain (OR: 1.05, 95% CI: 1.01;1.19), appetite loss (OR: 1.13, 95% CI: 1.07;1.18) and fatigue (OR: 1.20, 95% CI: 1.14;1.26), of having a higher total number of symptoms/problems (OR: 1.07, 95% CI: 1.02;1.113) and a higher number of severe symptoms/problems (OR: 1.12, 95% CI: 1.07;1.18), respectively. Results from the multiple linear regression showed the magnitude of these differences between patients referred by the general practitioners and hospital physicians was all <5 points on a 0-100-point scale for the level of symptoms/problems and 0.1 on a 0-9-point scale for the number of symptoms/problems, and thus, probably not clinically relevant.

The second research question in Paper 3 was *'Does the association between referral sector and symptoms/problems vary with the type of SPC (outpatient or inpatient) the patients are referred to?'*. For nine of the 10 symptoms/problems as well as for the total number of symptoms/problems and number of severe symptoms/problems, the odds ratios did not differ for patients referred to outpatient and inpatient SPC, respectively. For physical function, a statistically significant, but not clinically relevant, difference was found.

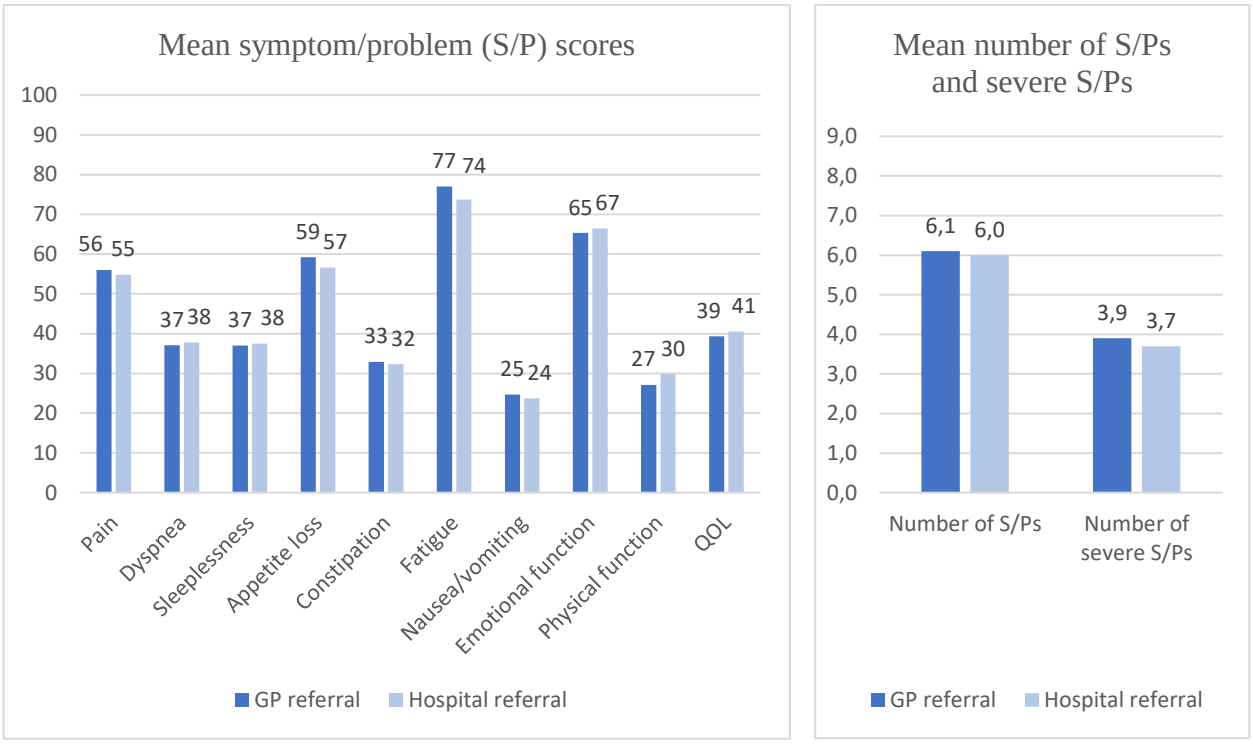

Figure 4: Mean symptom/problem (S/P) scores, mean number of symptoms/problems and mean number of severe symptoms/problems in patients referred by the general practitioner (GP) and physicians at hospitals, respectively.

Paper 4

The first research question in Paper 4 was *'Is the level of symptoms and problems at the start of SPC associated with survival time?'*. For all patients, the average survival time from start of SPC was 111 days and the median survival time was 49 days. The survival time was shorter for hospice patients (mean: 50 days, median: 20 days) compared to PCT patients (mean: 125 days and median: 59 days). In the backwards stepwise selection, age, sleeplessness (in PCTs), nausea/vomiting (in hospices), constipation and QOL were removed from the Cox regression model. Thus, in both of the final Cox models, seven out of ten symptoms/problems were significantly associated with survival time (Table 5). Higher levels of pain (only in hospices), dyspnea, appetite loss and fatigue as well as reduced physical function were significantly associated with increased risk of *short* survival time (Table 5). In contrast, worse emotional function and higher levels of pain (only in PCTs) and nausea (only in PCTs) were associated with an increased probability of *longer* survival time (Table 5). However, except for physical function, the associations were small (hazard ratios close to one). Better physical function was associated with a lower risk of short survival time. The risk of short survival in e.g., patients who on average experienced 'a little' physical function

problems was 68% of the risk of short survival in patients who experienced ‘quite a bit’ physical function problems on average.

Table 5: Hazard ratios (HRs) with 95% CI and p-value for one category worse symptoms/better function (33-point increase) in palliative care teams (PCTs) and hospice, controlled for the effect of gender, cancer site and type of patient (inpatient vs. outpatient) from Cox regression analyses.

	PCTs (N=23,143)		Hospice (N=5,538)	
	HR	95% CI	HR	95% CI
Pain	0.94	(0.93-0.96)	1.06	(1.03-1.09)
Dyspnea	1.09	(1.08-1.11)	1.07	(1.05-1.10)
Sleeplessness	-	-	1.05	(1.02-1.08)
Appetite loss	1.13	(1.12-1.15)	1.08	(1.05-1.11)
Fatigue	1.06	(1.04-1.09)	1.07	(1.02-1.12)
Nausea/vomiting	0.98	(0.96-1.00)	-	-
Emotional Functioning	1.09	(1.07-1.11)	1.07	(1.04-1.11)
Physical Functioning	0.68	(0.66-0.69)	0.68	(0.65-0.72)

The second research question in Paper 4 was: *'Does information on symptoms/problems make survival prediction more accurate than prediction based solely on* clinical variables?'. The overall accuracy for prediction of one-week- and one-month-survival, expressed by the area under the receiver operating characteristic (ROC) curve (AUC) was 0.76-0.84 for models including all variables from the final Cox model (Model 1, Table 6). AUC was reduced to 0.61-0.69 for models including only clinical variables (Model 2, Table 6). Almost the same AUC values as for model 1 were obtained by models including clinical variables and physical function as the only symptom/problem (Model 3, Table 6) and for models including only physical function (Model 4, Table 6). AUC was similar (for hospice) or higher (for PCTs) for models including only physical function (Model 4) compared to models including only clinical variables (Model 2).

Table 6: Area under the ROC curve from logistic regression for one-week and one-month survival prediction for models 1-4, separately for hospice and palliative care team (PCT).

	AUC			
	PCT		Hospice	
Explanatory variables in model 1-4	One-week	One-month	One-week	One-month
Model 1: clinical variables (gender, inpatient/outpatient and cancer site) and pain, dyspnea, sleeplessness*, appetite loss, fatigue, nausea/vomiting**, emotional function and physical function	0.84	0.76	0.76	0.76
Model 2: clinical variables	0.64	0.61	0.66	0.69
Model 3: clinical variables and physical function	0.82	0.75	0.74	0.75
Model 4: physical function	0.80	0.73	0.70	0.70

***only in palliative care team models, **only in hospice models**

Discussion

Discussion of main findings

To my knowledge, Paper 1 was the first study ever conducted to investigate whether the symptomatology was different, e.g. less severe (i.e., lower symptom scores/higher function scores) in SPC units with lower response rates compared to SPC units with high response rates, possibly indicating (more) selection bias in SPC units with low response rates. We found mainly similar symptom/problem-scores in SPC units with high response rates (≥60%) and SPC units with lower response rates and thus no indication of (more) biased symptom/problem-scores in SPC units with low response rates. One difference between SPC units with high and lower response rates at 5.7 points (in nausea) was, however, at the borderline of the level for clinically relevance (i.e., ≥5 points on a 0-100-point scale). The overall finding of no clinically relevant associations between response rate and symptom/problem-scores in Paper 1 is in line with the findings in a study of 304 patients admitted to an SPC unit where no clinically relevant differences between observed symptom/problem-scores and imputed scores were found, i.e., non-response did not seem to cause biased symptom/problem-scores [101]. The conclusion drawn from Paper 1 made it preferable to use the full data set in Papers 2-4 to make nationwide investigations of the symptoms/problems among patients admitted to SPC trusting that the symptom/problem-scores were as representative as possible of the national SPC population. Again, it should be acknowledged that there is a proportion of patients who cannot respond and who may have worse scores than those who were compared here: our conclusions are restricted to the comparison of units with high (≥60%) vs. lower response rates.

In Paper 2, the symptoms/problems reported at the most severe levels were fatigue, poor physical function, poor QOL, appetite loss, and pain. Although, the symptomatology differed for some symptoms/problems according to gender, age and cancer diagnoses, fatigue, poor physical function, poor QOL, appetite loss, and pain were consistently among the most severely rated symptoms/problems. Previous studies of patients referred to SPC have also reported that fatigue, pain, appetite loss, poor physical function and poor overall QOL were among the most frequent and severe symptoms/problems reported [36, 48-61, 63]. Patients admitted to SPC are severely ill and the symptomatology found in this study fits well with what was already back in the late 1980's described as the 'common terminal pathway', i.e., that cancer patients in the terminal phase will

experience symptoms related to malnutrition and poor physical function independently of cancer sites [102]. This symptomatology seems to be characteristic for advanced cancer patients admitted to SPC approaching death.

Concerning gender, women had a higher risk of nausea compared to men. Different factors might explain this, e.g., that women in general are more likely to have nausea and vomiting [103], that chemotherapy is used more often in treatment of female cancers or that women compared to men, because of their gender, are at higher risk of chemotherapy-related nausea and [104-108], or that anti-emetic drugs are less effective in women [109]. Several age differences were found; the most pronounced were poorer physical function, but less pain, less sleeplessness and better emotional function with increasing age. The poorer physical function in the older is not surprising since increasing age in general is associated with reduced physical function, which, according to this study, is also found in the population of advanced cancer patients nearing death who are referred to SPC. However, in a much smaller previous study of 278 patients referred to SPC, age was not significantly associated with physical function [36].

The lower risk of pain with increasing age found in our study might be explained by the assumption that older people have adapted to their body not functioning as well as it once did and thus not perceiving the same level of pain as severe as an 'unadapted' younger person would [110, 111]. This study, as well as some [52, 65] but not all [36, 48] previous studies of patients referred to SPC, found an increased risk of sleeplessness and poor emotional function in younger patients which might reflect that it may be more stressful for younger persons to cope with a life with terminal illness and imminent death [112].

Concerning diagnosis, large differences in the mean level and risk of symptoms/problems were found across cancer diagnoses, especially in dyspnea, appetite loss, pain and nausea. As expected the highest risk of dyspnea was found in lung cancer patients, and this has been reported by most previous studies with self-reported symptoms/problems in cancer patients referred to SPC [51, 56, 65], although in one study dyspnea in lung cancer patients was no significantly worse [36].

The highest risk of nausea was reported by patients with gastro-intestinal and gynecological cancers (stomach, small intestine and ovary cancer), and this was also found by some of the previous studies on cancer patients referred to SPC, which found the highest levels of nausea/vomiting in gynecological, esophagus and gastro-intestinal cancer [51, 56], although one study found no significant association between cancer diagnosis and nausea [36]. The position of the tumors in gastro- intestinal cancers can cause disruptions in the digestive system, e.g., bowel slowdown or blockage and constipation, which might explain the increased risk of nausea in

stomach and small intestine cancer patients found in this study [113, 114]. The high risk of nausea in ovarian cancer might be explained by metastasis, opioid treatment, chemotherapy used to treat the gynecological cancers, or that women in general are more likely to experience nausea and vomiting [104-108, 114].

In this study, the most severe and highest risk of appetite loss was in stomach, pancreas and esophagus cancer. This seems logical because these patients are likely to experience pain when eating and/or to have digestive problems because of tumor position, operations or imbalance in digestive hormones and enzymes [115-117]. Esophagus, stomach, colorectal and pancreas cancer patients were also most likely to experience anorexia and weight loss in previous studies on cancer patients in SPC [51, 56].

The highest pain levels were reported in patients with genital and urinary system cancers (bladder, prostate, and cervix cancer), multiple myeloma and sarcoma. Our results are in line with a previous study of patients referred to SPC where the highest risk of moderate/severe pain was found in prostate, gynecological, and head and neck cancer patients [56], but other studies did not find a significant association between diagnosis and pain [36, 51, 65]. Pain is common in advanced multiple myeloma and sarcoma patients [118]. The high risk for pain as well as constipation in prostate and bladder patients in this study could reflect that these patients receive more pain relieving medicine which is a known risk factor for constipation [119, 120].

In this study, brain/CNS cancer generally had the lowest symptom scores but at the same time a very poor physical function. The poor physical function is probably explained by trouble walking, trouble doing daily activities, problems with balance, seizures or paralysis caused by the brain tumors [121].

In Paper 3, it was concluded that patients referred to SPC by the general practitioner and patients referred by physicians in hospitals had similar symptomatology. This is reassuring because it supports the hope that overall (on average), physicians in the primary and secondary health care sector have a shared understanding of the symptom/problem-level needed for a SPC referral, are equally aware of the symptoms/problems troubling their patients and have the same level of competences and willingness to treat and help patients with advanced cancer. Clearly, the lack of differences in mean scores between sectors may hide underlying differences in characteristics between individual physicians as well as between sectors, but the important result is that we did not evidence of large, systematic differences in symptom/problem between sectors.

However, independently of who referred the cancer patients to SPC, the SPC referral took place late in the disease trajectory and therefore at a point where the patients experienced severe levels of symptoms as shown in Paper 2. Thus, perhaps the patients could have benefitted from an earlier referral to SPC. That would be sensible since palliative care, according to recent systematic reviews, has been found to be associated with improvement of symptoms/problems in advanced cancer patients [69, 70]. Palliative care early in the disease trajectory is also recommended by the American Society of Clinical Oncology, i.e., alongside active cancer treatment [122], and integration of palliative care and oncology has been recommended in a recent extensive report from a Lancet Oncology Commission [123].

Paper 4 found a short survival time in cancer patients admitted to SPC. Thus, 49 days after admittance to SPC half of the patients had died and the average survival time was 111 days. Furthermore, Paper 4 found the level of most symptoms/problems to be associated with survival time. Dyspnea, appetite loss, fatigue and low physical function were associated with an increased risk of short survival time in PCTs and hospices. This was expected since they all reflect poor health and in addition because previous systematic reviews of survival prediction in advanced cancer patients with expected survival of $\leq$ 3 months also found this [78-80]. Moreover, as mentioned previously poor physical function and signs of malnutrition was already back in the late 1980's suggested to be a 'common terminal pathway', i.e., characterizing patients nearing death. It is not surprising either that pain was associated with shorter survival in hospice patients.

It was, however, unexpected that the probability of longer survival time increased with worse emotional function and with increasing pain (only in PCTs) and nausea (only in PCTs). One explanation of this could be that patients with anxiety and depression and severe levels of pain and nausea are referred to SPC early. In this case, the symptoms and problems would not prolong survival time, but it would prolong the time from start of SPC to death (i.e., lead time bias). The early SPC referral would often be to PCTs which might explain why increased levels of nausea and pain were significantly associated with longer survival only in PCTs. The slightly increased probability of longer survival with higher levels of nausea/vomiting could, alternatively, be explained by a small proportion of the patients admitted to SPC are still receiving curative chemotherapy and perhaps these patients survive a little longer but at the same time they experience more nausea/vomiting.

Sleeplessness was associated with shorter survival time, but one could consider the possibility that it was not sleeplessness in itself, but rather the cause of sleeplessness (e.g., other symptoms or

delirium) that was associated with the reduced survival time. Several previous studied of patients referred to SPC did not find a significant association between sleeplessness and survival time [36, 66, 82, 83, 86, 89, 92, 124-128].

Concerning prediction of one-week and one-month survival, Paper 4 found that information on symptoms/problems, especially information on physical function, improved the overall accuracy (AUC level) of survival predictions when added to models including clinical variables only (i.e., gender, cancer diagnosis, and type of patient (inpatient vs. outpatient)). Interestingly, almost the same prognostic value was obtained by physical function alone as for all symptoms/problems combined. Therefore, if symptoms/problems are to be used clinically by physicians in their prognostications in the simplest possible way, the main focus should be on physical function. Furthermore, the predictive value of physical function was just as good as (in hospice) or better (in PCTs) than the predictive value of all the available clinical variables combined. This interesting finding based on our large study is in line with a much smaller previous study, which found performance status to be the most important variable in estimating survival time and also found that clinical variables (gender, age and cancer site) could not improve the estimation of survival time when added to a model including performance status [129].

In Paper 4 it was, however, also concluded that the predictive value of physical function and/or symptoms/problems was probably not good enough to be of clinical value. The patient's physical function should be taken into account when clinicians make prognostications, but the information about the level of physical functioning needs to be supplemented by other information if survival predictions are to become more accurate. It does, however, require more research to decide which factors would increase the predictive value most if added to a predictive model with physical function. In this study the focus was solely on the prognostic value of symptoms/problems and clinical variables, but previous studies developing prognostic tools for survival prediction in patients in palliative care (e.g., the Palliative Prognostic Score (PaP) and the Palliative Prognostic Index (PPI)), also found other factors such as the physicians' clinical predictions, biological factors (total white blood cell count and lymphocyte percentage), and delirium important in survival prediction [84, 85]. It is also possible that the change in symptom/problem-level in the first weeks after SPC admittance would have high predictive value, but that also needs further investigation.

Methodological strengths and limitations

The findings provided in this PhD thesis about the symptomatology of cancer patients at the start of SPC and factors related to the symptomatology, are important contributions to the existing

research field of symptomatology in cancer patients referred to SPC. Several reasons for the importance of the knowledge gained from Papers 1-4 can be mentioned: the study populations of Papers 1-4 were the largest to date, the studies were nationwide and based on data from all Danish SPC units including hospice and hospital- and home-based palliative care teams. Furthermore, the information on the symptoms/problems was systematically obtained at the start of SPC for all patients, the symptoms/problems were patient reported (i.e., unbiased by proxy reporting from health professionals or family) by using a validated tool adapted to cancer patients in palliative care (EORTC QLQ-C15-PAL), and a well-defined time window (0-3 days before admission) for the patient-reporting was used.

Because of the very large study population random error, i.e., that the study findings are due to 'chance' seems unlikely. On the other hand, interpretation of statistically significant findings should be done cautiously as the large sample increases the statistical strength to a point where significant findings may be too small to be of clinical significance.

Information on all variables in this PhD thesis was obtained from the DPD where almost all patients referred to SPC since January 1st, 2010 are registered and the data completeness for most variables is close to 100% [18]. The completeness of the data in DPD is assured because most information is mandatory to report and missing answers as well as 'strange' answers are continuously checked and corrected [18]. Therefore, for the patients included in Papers 2-4, i.e. those reporting their symptoms/problems at the start of SPC, information on clinical variables was complete to a very high extend.

In the following possible limitations in Papers 1-4 will be discussed. Even though the Danish Palliative Care Database (DPD) includes almost all patients admitted to SPC from January 1st, 2010 [18], selection bias is possible because only 56% of all cancer patients admitted to SPC were included, i.e., only those who reported their symptoms/problems at the start of SPC.

When those who answered EORTC QLQ-C15-PAL (i.e., the study population) were compared to non-respondents, a similar mean age and gender distribution was found and thus there was no evidence of selection bias in relation to gender and age. There were, however, differences in the distribution of diagnoses between respondents and non-respondents and because of lower response rates for patients with leukemia, lymphoma, brain and CNS cancer as well as patients with 'unknown cancer site' compared to patients with the remaining cancer diagnoses, these diagnoses were slightly underrepresented in the study population. This should be noted, but the impact of this slight underrepresentation is probably minimal as these diagnoses are relatively rare.

Inpatients, hospice patients and patients with short survival were also underrepresented in the study population. It is likely that the lower response rate in inpatients, hospice patients and short time survivors was (partly) due to poor health. The underrepresentation of inpatients, hospice patients and patients with short survival time in the study population will probably result in too low overall symptom/problem mean scores i.e., an underestimate of the severity and prevalence of symptoms/problems.

In Paper 1, it was investigated whether there were indications of more impact of selection bias in SPC units with low response rates compared to SPC units with high response. We did this because one could suspect that in SPC units with low response rates, the EORTC QLQ-C15-PAL questionnaire was only distributed to the most well patients because they were the easiest to obtain the symptom/problem reporting from and/or because clinicians did not want to bother the most ill patients with the questionnaire. Therefore, Paper 1 tested the hypothesis: *only the most well patients reported their symptoms/problems in SPC units with low response rates*. No indication of such (additional) selection bias in SPC units with low response rates was indicated since comparisons of the symptom/problem-levels between the SPC units with the highest response rate (≥60%) and SPC units with lower response rates only found small significant mean differences, i.e., they were not clinically relevant, although one difference in nausea was at the borderline of clinical relevance. To design an analysis to test our research question, we had to assume that the symptom/problem-scores in SPC units with the highest response rates (≥60%) were the most representative for patients admitted to SPC capable of reporting their symptoms/problems, which is of course not certain, but we believed the lowest probability of biased scores were in the SPC units with the highest response rates and in palliative care it would probably be difficult to get much higher response rates because of the poor health of the patients.

The symptomatology in this PhD thesis was assessed by EORTC QLQ-C15-PAL, which was developed and validated in cancer patients in SPC [25]. Because the symptoms/problems were assessed systematically at the start of SPC (and not on one of the following days where symptoms/problems may have been modified by treatment and care) and by the patients themselves (as opposed to assessed by health care professionals) the likelihood of valid and comprehensive symptom assessment is increased [21-23, 47]. The EORTC QLQ-C15-PAL is a short questionnaire minimizing the patient burden of symptom reporting which is important in a population of very ill patients. However, due to the shortness of the questionnaire, it is of course

not possible to assess all the symptoms and problems patients admitted to SPC might experience and less frequent symptoms that may be very distressing for patients have not been investigated in this PhD thesis. Small supplementary, questionnaires used together with EORTC QLQ-C15-PAL could help to ensure all the symptoms patients are bothered by are reported. This is elaborated in the 'Perspectives' section.

Concerning the statistical analyses, Papers 1-4 all used multivariate analyses, where relevant possible confounders were included so they would not distort the associations studied. Of course, we could only control the analyses for variables we had access to in DPD which, e.g., did not include socioeconomic variables known as common confounders in health research.

In Paper 4 it would have been interesting to include information on e.g. biological variables such as laboratory tests because they might help predict survival time. In paper 3 it could have been relevant with a more detailed classification of who referred the patient to SPC by e.g., subdividing physicians according to their specialty.

Paper 3 is to my knowledge the first to investigate if the symptomatology at the start of SPC differed by referral sector (i.e., general practitioners and hospitals physicians). This was one way to investigate if patients with the same level of symptoms had the same access to SPC across health care sectors. This could and should be investigated in other ways, for example by investigation reasons for referral and non-referral to SPC among physicians in the primary compared to physicians in the secondary health care sector. Factors such as perceived level of competences in relieving symptoms and providing palliative care, wish for and capacity to handle patients with complex symptomatology in the non-SPC hospital units and in general practice, availability and perceived quality of the work of SPC units, etc., could be reasons for referral (and non-referral) to SPC [74, 75, 130] and these factors may or may not be similar across health care sectors. One could also speculate that differences in reasons for referral and non-referral to SPC were not dependent on the health care sector but rather on differences among physicians on the individual level [131, 132]. Is was, however, not possible to include information at the individual level of referring physicians in Paper 3 since such information was not available in DPD.

When considering the generalizability of study findings to other populations it is important to remember that the study findings might not be applicable to patients with very short survival time

from start of SPC. The studies in this PhD thesis were conducted in Denmark and included cancer patients from all the SPC units in the country, i.e., all types of SPC units. Many of the findings can probably be generalized to cancer patients admitted to SPC in other Western countries but one must be aware that there may still be important differences between countries due the organization of health care systems, SPC services, referral criteria, and education of various groups of physicians and other health care professionals. In particular, it is unknown whether findings regarding the association between the type of referring physician (i.e., general practitioner or physician at a hospital) and symptoms/problems may be generalized to other countries due to differences in which health professionals the cancer patients see at what time in their disease trajectory, the level of education in palliative care at the basic level, how physicians referring patients to SPC perceive the quality of SPC, and how they collaborate with the SPC units. Whether the findings from Papers 1-4 can be generalized to patients with other diagnoses than cancer is unknown and needs to be investigated in future studies.

Conclusions

- Almost no clinically relevant differences were found in the levels of the symptoms/problems between SPC units with the highest response rates (≥60%) and SPC units with lower response rates. Therefore, no large impact of selection bias was apparent in SPC units with low response rates compared to SPC units with high response rates. Therefore, in future studies of national datasets, there does not seem to be any reason to exclude data from SPC units with low response rates (Paper 1).
- Cancer patients are severely troubled by symptoms such as fatigue, appetite loss and pain as well as impaired physical function and reduced overall QOL at the start of SPC (Paper 2).
- Gender, age and cancer diagnoses, respectively, were significantly associated with most symptoms/problems. The strongest associations between symptoms/problems and gender and age, respectively, were the higher risk of nausea in women as well as the higher risk of poor physical function and lower risk of sleeplessness, pain and poor emotional function with increasing age. The largest differences in mean scores between diagnoses were in dyspnea, appetite loss, pain and nausea (Paper 2).
- The differences in the number and severity of symptoms/problems for patients referred by the primary and secondary health care sectors (i.e., general practitioners compared to hospital physicians) were small and thus, probably not clinically relevant. This is reassuring since it suggests that there may not be any major difference in access across health care sectors for patients with similar need for symptom relief (Paper 3).
- Pain, dyspnea, sleeplessness (only in hospice), appetite loss, fatigue, nausea/vomiting (only in palliative care teams), emotional function and physical function were significantly associated with survival time. The associations were, however, small, except for physical function (Paper 4).
- Adding symptoms/problems, especially physical function, to prediction models including only clinical variables (i.e., gender, cancer diagnoses, inpatient vs. outpatient) increased the overall accuracy of one-week and one-month survival predictions, but such models are still not precise. Physical function was the symptom/problem with the highest predictive value and therefore, the focus should be on physical function if symptoms/problems are to be used for survival prediction in clinical practice (Paper 4).

Perspectives

Even though this PhD thesis has shed light on the symptomatology of Danish cancer patients at the start of SPC, further research in the symptomatology of patients at the start of SPC is relevant in order to expand the knowledge of symptomatology in patients at the start of SPC. The natural next research steps could be:

- to study how the level of symptoms/problems at the start of SPC are associated with other factors, e.g., socioeconomic factors, risk of later hospitalization in non SPC-units, and place of death.
- to study how the level of symptoms/problems changes from the start of SPC (to what extent they improve following SPC), and if the change is associated with variables such as cancer diagnoses, type of SPC, and other variables studied here, etc.
- to study what the main reasons for SPC referral are and if they are similar for general practitioners and physicians in hospitals.
- to study if other variables (such laboratory variables, e.g. markers of inflammation) could improve survival prediction from start of SPC when added to prediction models including physical function.
- to repeat the same research questions as in this PhD thesis but in patients with other diagnoses than cancer, e.g., heart diseases, renal diseases, chronic obstructive pulmonary disease, neurological diseases etc.

Today, studies in palliative care patients have documented the importance of patient reported outcomes (as opposed to assessments by health care professional) assessed systematically by symptom assessment tools in order to comprehensively detect patients' symptoms [21-23]. This was also recognized in a recent report from the Danish Health Authorities, where it was underlined that an important element of a palliative needs assessment is the patients' own experience of their symptoms and QOL, i.e., patient reported outcomes (PRO) which EORTC QLQ-C15-PAL could be used to obtain [15]. In the report it was recommended that the need of palliative care was assessed when a patient receives a life-threatening diagnosis (e.g., cancer or chronic obstructive pulmonary disease) and continuously assessed, especially when the disease progresses and when the patient crosses between health care sectors [15]. Thus, with the aim of better patient centered care, the Danish Health Authorities recommended that PRO were obtained not only in SPC (i.e.,

the tertiary health care sector) but also in the primary and secondary health care sector, starting at the point where a patient is diagnosed with a life-threatening disease [15].

In 2015, the Danish Ministry of Health and Prevention introduced 'learning and quality teams' as a part of the new Danish quality model of health and underlined the importance of patient centered care and the use of PRO in the health care system [133]. The first learning and quality team project was *'Learning and quality teams -palliation*. The *'Learning and quality teams -palliation'* project aimed at improving the QOL of patients admitted to SPC (and their families). A part of the project was to use the PRO reported on EORTC QLQ-C15-PAL by patients admitted to SPC systematically in the clinical care of patients in SPC units. This was done by releasing 'packages' (e.g., a 'pain package') when a patient experienced at least 'quite a bit' of pain, dyspnea, constipation or depression. A 'package' consisted of different types of care, including pharmacological and non-pharmacological care, recommended by relevant clinical guidelines which should be given to the patients (and relatives) when it was relevant. Data from this project are to be evaluated and it will be interesting to see if the systematical use of PRO in patient-care (and the other quality improvement initiatives in the project) did improve the QOL of patients admitted to SPC.

The importance of using PRO in the Danish health care system in general was also underlined by the financial agreement for 2017 between the Danish state and regions where it was decided that PRO-data should be developed at a national level and used in all sectors of the health care system [134]. By expanding the use of PRO in the health care system, the aim was to: improve patient centered care, to improve the treatments, to improve the patients' experience of the health care system and to improve continuous patient care across the health care system by improving communication across health care sectors [135]. At the moment, as a part of the expansion of PROs in the Danish health care system, the Danish health directors are interested in how PRO can be expanded in palliative care. If the use of PRO is to be expanded in palliative care, it can be discussed how extensively it should be done and how it should be implemented. Today, PRO is used for all diagnoses in SPC (i.e., in the tertiary health care sector) by systematic assessment of symptoms/problems using EORTC QLQ-C15-PAL. This could be expanded to the secondary and perhaps also the primary health care sector for cancer patients or also for other diagnoses (Table 7).

Table 7: PRO (patient reported outcomes) tool used systematically today according to health care sector, level of palliative care and disease.

Health care sector **Level of palliative care**	Primary **Basic**	**Secondary** **Basic**	**tertiary** **Specialized**
Disease			
Cancer	PRO tool*: To be decided	PRO tool*: To be decided	PRO tool*: EORTC QLQ-C15-PAL and WISP
Non-cancer **Heart diseases** **Lung diseases** **Kidney diseases etc.**	PRO tool*: To be decided	PRO tool*: To be decided	PRO tool*: EORTC QLQ-C15-PAL and WISP

PRO: Patient reported outcomes

The Danish Health Authority has recommended the same PRO tool to be used across health care sectors [15], and given the experience in the tertiary sector, the EORTC QLQ-C15-PAL may be an obvious choice of tool. If EORTC QLQ-C15-PAL is to be used as a national tool across diagnoses and health care sectors a few things are worth considering. First, EORTC QLQ-C15-PAL was developed and validated in cancer patients, i.e., not patients with other diagnoses [25], and thus, perhaps it would be an improvement for patients with other diagnoses if EORTC QLQ-C15-PAL was expanded or supplemented with small extra disease specific questionnaires. This is, however, only relevant if EORTC QLQ-C15-PAL does not assess the most common and severe symptoms/problems for other diseases, e.g., for heart diseases, lung diseases and kidney diseases. Another consideration is that no questionnaire will be able to assess all symptoms/problems, and one could argue that it is a limitation of EORTC QLQ-C15-PAL that it does not assess spiritual and existential problems which are central elements in palliative care. Therefore, it might be an improvement of EORTC QLQ-C15-PAL if it was expanded to assessing these problems as well, but of course only if meaningful questions could be developed. On the other hand, one could argue that all patients faced with life-threatening disease would benefit from a talk with health care professionals (or other professions) about spiritual and existential issues and thus all should have such a talk which may make assessment of these problems redundant. If the EORTC QLQ-C15-PAL questionnaire is not assessing all important symptoms/problems experienced by cancer

patients and/or patients with other diagnoses a solution to this problem could be to supplement EORTC QLQ-C15-PAL with the WISP (Write In three Symptoms/Problems) instrument which is already done in SPC today. WISP consists of three open ended questions where patients' have the possibility to report three extra symptoms after they have filled in the EORTC QLQ-C15-PAL questionnaire and thus hopefully no important symptoms/problems go undetected. Analyses of data from WISP have been initiated and more work is needed.

Summaries

English summary of the PhD thesis 'Symptoms and Problems in Cancer Patients Admitted to Specialized Palliative Care'.

Introduction: Many patients with advanced cancer experience symptoms and problems, and some patients will be admitted to specialized palliative care (hospice or palliative care teams/units in hospitals) for symptom relief in the last part of their lives (often the last weeks to months). Previous studies of cancer patients at the start of specialized palliative care (SPC) have typically been small and in a single specialized palliative care unit. This PhD thesis studied symptoms, problems and overall QOL in cancer patients at the start of SPC at the population level, using nationwide data from all SPC units in Denmark aggregated in the Danish Palliative Care Database (DPD).

Aims: About 50% of the patients admitted to SPC filled in the EORTC QLQ-C15-PAL questionnaire at the start of SPC. The aim of Paper 1 was to test whether symptom/problem-scores differed between SPC units with the highest and lowest response rates, indicating a possible selection bias in SPC units with low response rates. Paper 2 investigated the levels of symptoms and problems in patients at the start of SPC and how gender, age and cancer diagnosis were associated with the levels of symptoms/problems. Paper 3 investigated whether the levels of symptoms/problems differed for patients referred by general practitioners and by physicians at hospitals. Lastly, Paper 4 studied if symptoms/problems were associated with survival time from start of SPC and whether taking symptoms/problems into account could improve one-week and one-month survival prediction.

Patients: Cancer patients admitted to SPC who died between 2010-2017 and who reported their symptoms and problems at the start of SPC using the EORTC QLQ-C15-PAL questionnaire.

Statistical methods: In Paper 1, multiple linear regression analysis was used to compare symptom/problem-scores for the SPC units with the highest response rates to scores for SPC units with lower response rates. In Papers 2-3, ordinal logistic regression was used to study the associations between symptom/problem-scores and gender, age and cancer diagnoses, respectively (Paper 2), or referral sector (Paper 3). In Paper 4, Cox regression was used to study the associations between symptoms/problems and survival time; furthermore, logistic regression analyses with one-week and one-month survival as outcomes were used to test the predictive value of clinical variables and symptoms/problems.

Results: In Paper 1, no clinically relevant differences were found in symptom/problem-scores between SPC units with the highest and lower response rates and therefore there was no indication of selection bias. Paper 2 found severe levels of symptoms/problems in cancer patients at the start of SPC. The most severe symptoms/problems were pain, appetite-loss, fatigue, poor physical function and poor QOL. The strongest associations between symptoms/problems and gender and age, respectively, were the increased risk of nausea in women as well as the increased risk of poor physical function and reduced risk of sleeplessness and pain with increasing age. Cancer diagnosis was significantly associated with all symptoms/problems. Paper 3 found that associations with referral sector were generally small and thus probably not clinically relevant. Paper 4 showed that physical function was the symptom/problem with the strongest association to survival time. Symptoms/problems (especially physical function) improved the overall accuracy for one-week- and one-month survival prediction.

Conclusions: There was no indication that the scores for symptoms and problems from SPC in units with low response were affected by selection bias. The cancer patients admitted to SPC were severely troubled by symptoms and problems. Gender, age and cancer diagnosis were significantly associated with most symptoms and problems, but the strength and direction of the association were dependent on the symptom/problem. Similar levels of symptoms/problems were found for patients referred by general practitioners and physicians at the hospitals. Most symptoms/problems were associated with survival time and inclusion of symptoms/problems improved prediction of one-week and one-month survival.

Dansk resume af Ph.d.-afhandlingen 'symptomer og problemer blandt kræftpatienter modtaget til specialiseret palliativ indsats'.

Introduktion: De fleste kræftpatienter vil takt med, at deres sygdom forværres opleve forskellige symptomer og problemer og nogle patienter vil i den sidste del af deres liv (ofte de sidste uger til dage) få behov for specialiseret palliativ indsats (SPI) til at afhjælpe deres symptomer og problemer enten på et hospice eller i palliative teams på hospitaler eller i eget hjem. Tidligere studier, der har undersøgt symptomer/problemer blandt kræftpatienter ved start af SPI, har ofte inkluderet et begrænset antal patienter og ofte kun patienter fra en enkel SPI-enhed. I denne ph.d.-afhandling er der anvendt landsdækkende data fra Dansk Palliativ Database på patienter fra alle SPI-enheder i Danmark til at undersøge symptomer, problemer og samlet livskvalitet blandt kræftpatienter ved start af SPI.

Formål: Omkring 50% af de kræftpatienter, der blev modtaget til SPI udfyldte et EORTC QLQ-C15-PAL-spørgeskema ved modtagelsen. Formålet med artikel 1 var at undersøge, om der var forskel i symptom/problem scorerne i SPI-enheder med de højeste svarprocenter sammenlignet med SPI enheder med lavere svarprocenter, idet en forskel kunne være et udtryk for selektionsbias i enhederne med lavere svarprocenter. Artikel 2 undersøgte graden af symptomer og problemer ved start of SPI blandt kræftpatienter og betydningen af køn, alder og kræftdiagnose for graden af symptomer/problemer. I artikel 3 blev det undersøgt, om der var forskel på graden af symptomer/problemer for patienter henvist til SPI af praktiserende læger sammenlignet med patienter henvist fra sygehusafdelinger. I artikel 4 blev sammenhængen mellem graden af symptomer/problemer og overlevelsestid undersøgt, herunder om viden om symptomer/problemer kunne øge præcisionen af 1-uges og 1-måneds overlevelsesprædiktioner.

Studiepopulation: Kræftpatienter, der blev modtaget til SPI og døde i perioden 2010-2017, og som der rapporterede deres symptomer og problemer ved start af SPI

Statistiske metoder: I artikel 1 blev de gennemsnitlige symptom/problem-scorer sammenlignet mellem SPI-enheder med de højeste svarprocenter og SPI-enheder med lavere svarprocenter ved hjælp af multipel lineær regression. I artikel 2 og 3 blev sammenhængen mellem symptomer/problemer og hhv. køn, alder og kræftdiagnose (artikel 2) samt henvisende instans (artikel 3) analyseret vha. ordinal logistisk regression. I artikel 4 blev sammenhængen mellem graden af symptomer/problemer og overlevelsestid undersøgt vha. Cox regression. Derudover blev den prædiktive værdi af symptomer/problemer undersøgt vha. logistisk regression med 1-uges og 1-måneds overlevelse som udfald.

Resultater: I artikel 1 blev der ikke fundet klinisk relevante forskelle i graden af symptomer/problemer for SPI-enheder med de højeste svarprocenter sammenlignet med SPI-enheder med lavere svarprocenter, og der var derfor ikke noget, der tydede på selektionsbias. Artikel 2 fandt et højt niveau af symptomer og problemer blandt kræftpatienter ved starten af SPI, og patienterne var i særlig høj grad belastet af smerte, appetitløshed, træthed, lav fysisk funktion og lav livskvalitet. De stærkeste sammenhænge mellem henholdsvis køn og alder og graden af symptomer/problemer, var en højere risiko for kvalme blandt kvinder og en øget risiko for dårlig fysisk funktion og lavere risiko for smerte, søvnløshed og dårlig følelsesmæssig funktion med øget alder. Artikel 3 fandt signifikante forskelle i graden af nogle symptomer/problemer for patienter henvist af praktiserende læge til SPI sammenlignet med patienter henvist fra sygehusafdelinger, men forskellene var små og sandsynligvis ikke klinisk relevante. Artikel 4 fandt, at fysisk funktion var det symptom/problem, der var stærkest associeret med overlevelsestid og at symptomer/problemer (specielt fysisk funktion) øgede præcisionen af 1-uge og 1-måneds overlevelsesprædiktioner.

Konklusion: Der var ikke nogen indikation af, at symptom/problem-scorerne fra patienter i SPI-enheder med lave svarprocenter var påvirket af selektionsbias. Patienter modtaget til SPI var alvorligt belastede af symptomer/problemer og der var en signifikant sammenhæng mellem henholdsvis køn, alder og diagnose og graden af de fleste symptomer/problemer, men styrke og retning varierede. Graden af symptomer og problemer var sammenlignelige for patienter henvist af henholdsvis praktiserende læge og af læger på hospitalsafdelinger. De fleste symptomer/problemer var associerede med overlevelsestid, og information om symptomer/problemer forbedrede 1-uges og 1-måneds overlevelsesprædiktioner.

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