Early integration of palliative care in oncology

Gaëlle Vanbutsele

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Strive not to be a success
but rather to be of value

Albert Einstein

Content

Chapters 2-7 are based on the following publications

Chapter 2:

Vanbutsele G , Pardon K, De Laat M, Jacobs C, Colman R, Loge JH , Hjermstad MJ , Kaasa S, Deliens L. Prevalence and variability of a positive screening for major depression in palliative care cancer patients. The longitudinal European Palliative Care Cancer Symptom study (EPCCS-study).

Chapter 3:

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Chapter 4:

Vanbutsele G, Van Belle S, De Laat M, Surmont V, Geboes K, Eecloo K, Pardon K*, Deliens L*. The systematic early integration of palliative care into multidisciplinary oncology care in the hospital setting (IPAC), a randomized controlled trial: The study protocol. BMC Health Serv Res 2015 Dec 15; 15:554. [2017 Impact Factor: 1.843, 2015 Impact Factor: 1.606, Journal ranking Q3]

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Chapter 6:

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Chapter 7:

Vanbutsele G, Van Belle S, Surmont V, De Laat M, Colman R, Eecloo K, Naert E, De Man M, Geboes K, Deliens L*, Pardon K*. The effect of early and systematic integration of palliative care in oncology on quality of life and health care use near the end-of-life: a randomized controlled trial. (Submitted)

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PART I

General introduction

Chapter 1:

General introduction

1.1. Introduction

Patients with advanced and incurable cancer typically suffer from a multitude of severe symptoms. Pain, fatigue, nausea/vomiting, dyspnea, constipation, loss of appetite and depression are among the most common symptoms[1–6]. Symptoms are often undertreated and one of the reasons is underdiagnosis: according to a European multicenter study, health care providers underestimate symptom intensity in one out of 10 patients with advanced cancer[7]. Reasons for this underdiagnosis are related to limited time to tend to patients, to a strong orientation of health care providers towards cure or life-prolongation rather than quality of life and to a lack of expert knowledge in symptom management[8–10]

Oncologists are at the center of the care of cancer patients, guiding treatment decisions with a particular focus on systemic treatments to control the cancer for as long as possible. The understanding of the biology of different cancers has remarkably increased and as a result also the number of new drugs available to target these diseases. This has intensified the complexities in cancer therapeutics and together with the raising number of patients diagnosed with cancer, has led to increased demands on oncologists[11]. It can be a daunting task for oncologists to present treatment options and potential side effects comprehensively and effectively to their patients while keeping sufficient time to address the numerous supportive care needs of patients, their understanding of their disease and treatment goals[12].

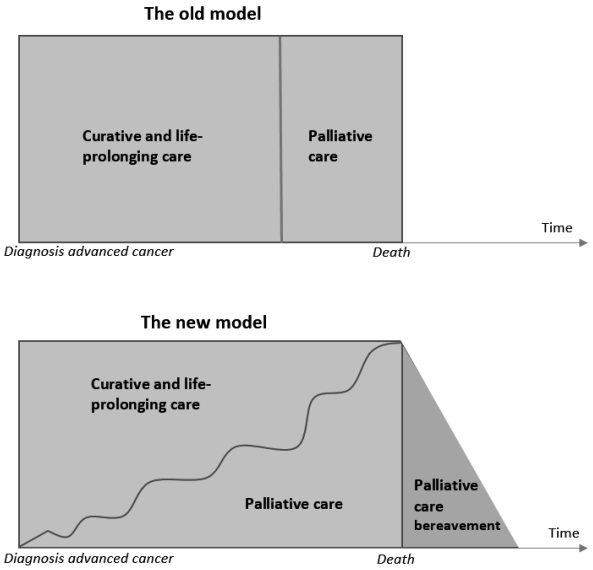
It has been suggested that integrating specialized palliative care within oncology care has the potential to address some of the gaps in the traditional model[13]. The World Health Organization (WHO) defines palliative care as '*an approach that improves the quality of life of patients and their families facing the problems 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*'[14]. The WHO stresses that palliative care is applicable early in the course of the illness, together with other therapies that are intended to cure or prolong life, such as chemotherapy or radiation therapy. The goals of palliative care, such as improving quality of life through comprehensive symptom management and patient and family support, should ideally be applied throughout the trajectory of a serious illness such as advanced cancer[15].

Figure 1 describes the new model of early-integrated palliative care; this model is different from the old model in which palliative care is seen as an attachment to the curative and life-extending phase. In the old model, palliative care is only initiated when there are no options left, often near the end-of-life[16]. Studies show that this old model is still frequently used in oncology. In Belgium, a survey shows that patients with advanced cancer were referred 16 days prior to death[17,18].

In the new model, palliative care starts at diagnosis and as the disease progresses, palliative care becomes increasingly important, though in a varying way, according to the patient's needs. This new model of care

allows oncology teams and palliative care clinicians to share in the complex tasks necessary to provide comprehensive care to patients with advanced cancer and their families. It also focuses on those persons who are caring for the patient[19,20].

Figure 1: the old and new model of early integrated palliative care in oncology care (adapted from the model of Lynn and Adamson[20])



There is accumulating scientific evidence that supports the value of this new model of early integration of specialist palliative care, i.e. the care that is provided by an interdisciplinary palliative care team, both in outpatient and inpatient settings[21,22].

Before addressing the specific research aims of this dissertation, the results of the randomized controlled trial (RCT) studies that were published at the start of this PhD research will be described. Those trials that tested the early and fully integrated specialist palliative care model and found positive results are discussed below. The results of trials that were published while conducting this study are described in the final chapter of this dissertation.

In the Project ENABLE (Educate, Nurture, Advise, Before Life Ends)[23], 322 patients who were newly diagnosed with advanced gastrointestinal, lung, genitourinary, and breast cancers were randomly assigned to receive a multicomponent nurse-led intervention in combination with usual care versus usual care alone.

The researchers developed a psycho-educational nursing intervention: an advanced practice nurse conducted four educational and problem-solving sessions with the patient and did monthly follow-up sessions.[9] Patients were also encouraged to contact the oncology team, palliative care team or other specialists themselves if they felt a need. The project was situated in United States[24].

Outcomes included quality of life measured by the Functional Assessment of Chronic Illness Therapy-Palliative Care, symptom intensity as per the Edmonton Symptom Assessment Scale (ESAS), mood using the Center for Epidemiological Studies Depression Scale, and resource use (i.e., days in the hospital and intensive care unit and number of emergency department visits). Patients assigned to the intervention reported significantly better quality of life (p=0.02), mood (p=0.02) as well as a marginally significant effect for symptom intensity (p=0.06). Authors did not report a group difference in resource use[23]. They concluded that early introduction of a palliative care intervention, concurrent with disease-modifying treatments, benefits patients with advanced cancer[23,24].

The landmark study of early palliative care is a single institution phase III randomized controlled study in 151 outpatients with metastatic non-small-cell lung cancer situated in Boston, United States. In this study, the effect of the intervention of 'early palliative care' integrated with standard oncology care was compared to standard oncology care alone (with no palliative care provision or only late in the disease course). The early palliative care intervention consisted of a consultation for patients with a member of the palliative care team of the hospital shortly after diagnosis of the advanced cancer and at least monthly thereafter. The palliative care team of the hospital comprised palliative care physicians and an advanced-practice nurse. The consultations were guided by newly developed palliative care guidelines that differed from the existing guidelines for standard palliative care: the palliative care clinicians were more specifically encouraged to assess physical and psychosocial symptoms throughout the disease trajectory, establish goals of care and assist with treatment decision-making and coordination of care.[11,25]. Table 1 gives an overview of the interventional palliative care guidelines.

Table 1: Interventional Palliative Care Guidelines

- Illness-understanding/education
Inquire about illness and prognostic understanding
Offer clarification of treatment goals
- Symptom management – inquire about uncontrolled symptoms
Focus depends on type of advanced cancer
- Decision-making
Inquire about mode of decision-making
Assist with treatment decision-making, if necessary
- Coping with life-threatening illness
Patient
Family/caregivers
- Referrals/prescriptions

Quality of life and mood were assessed at baseline and at 12 weeks. Change in quality of life at 12 weeks was the primary outcome of the study and this was measured by using the Functional Assessment of Cancer Therapy–Lung Trial Outcome Index (FACT-L TOI). Mood was measured with the Hospital Anxiety and Depression scale. Other outcome measures were aggressiveness of end-of-life care and survival. Patients were classified as having received aggressive care if they met any of the following three criteria: (1) chemotherapy within 14 days before death, (2) no hospice care or (3) admission to hospice three days or less before death[25].

Patients in the palliative care group had significantly higher quality of life scores compared with to the standard care group: a 2.3 point increase in mean TOI score from baseline to 12 weeks compared with a 2.3 point decrease in standard care group (p=0.04). The percentage of patients with depression at 12 weeks was significantly lower in the palliative care group than in the standard care group (16% versus 38%, p=0.01), while there was no difference between groups in scores for symptoms of anxiety. A group difference was found for aggressiveness of care: 33% of the patients who were assigned to 'early palliative care' compared to 54% of the standard oncology group had received aggressive end-of-life care (p=0.05). This study also reported a difference in median survival of 2.7 months (p=0.02) in favor of the intervention group. The authors concluded that early integration of palliative care for patients with metastatic non–small-cell lung

cancer is clinically meaningful and feasible, with effects on survival and quality of life that are similar to the effects of first-line chemotherapy in such patients[25].

A similar model of palliative care in the outpatient setting was tested in a cluster randomized controlled trial on 461 patients with different types of metastatic cancer, i.e. gastrointestinal, breast, lung, etc. in Canada[26,27]. The intervention consisted of consultations and follow-up in the oncology palliative care clinic by a palliative care nurse and physician, with a comprehensive, multidisciplinary assessment within 1 month of recruitment, routine telephone contact from a palliative care nurse 1 week after the first consultation, monthly outpatient palliative care follow-up and a 24-h on-call service for telephone management of urgent issues. Study measures consisted of quality of life (the Functional Assessment of Chronic Illness Therapy—Spiritual Well-Being and The Quality of Life at the End Life) , symptom severity (ESAS), satisfaction with care (FAMCARE P16) and problems with medical interaction (Cancer Rehabilitation Evaluation System Medical Interaction Subscale (CARES-MIS)). By 4 months, differences between groups were significant for all measures, expect CARES-MIS, in favor of the early palliative group. The authors concluded that these findings are consistent with those of previous studies showing that early palliative care improves quality of life and also the satisfaction of patients with their care [26].

1.2. Relevance of this work

The evidence on referral to specialized palliative care and early integration of palliative care in oncology described above has certain shortcomings.

Firstly, studies have examined the availability and timing of referral to specialized care in cancer and concluded that referral still occurs late in the disease trajectory[28–30]. However, these studies either perceived cancer patients as a homogenous group[29] or were often limited at an institutional level[28]. In addition, the reasons why physician did not refer to specialist palliative care services were not assessed or only mentioned in qualitative studies at the most[31] .To understand the level of integration of palliative care in oncology, it is important to conduct studies at the population level and examine if there are any inequalities in access to specialized palliative care[32].

In addition, many studies have examined symptom burden during the disease trajectory of patients with advanced cancer[33–36]. However, these are often only conducted within oncology or palliative care[37]. Evidence of symptom development in integrated palliative care in oncology is scarce[38,39]. Depression is a frequent psychiatric condition in advanced cancer and is known to have an important negative impact on quality of

life[40,41]. Studies of depression, however, most often relied on cross-sectional analysis techniques or were conducted prospectively but with a limited time scope[42,43]. Few studies of depression in palliative care have robust epidemiological longitudinal design which would aid in understanding the changing burden of depression over time and help to improve symptom management through comprehensive palliative cancer care.

Secondly, and more importantly, when starting this PhD research, few studies had examined the effect of early integration of palliative care in cancer care and all of them originated from North America[23,25,26]. , The published results of early integrated palliative care were promising[44]. However, before this new approach could become part of general clinical practice, this early palliative care approach had to be tested in different centers and most importantly in different countries where standard oncology care and/or palliative care may be different from that in the US or Canada.

1.3. Study objectives and research questions

The main objective of this dissertation is to gain insight in the challenges for and benefits of integration of palliative care in oncology. We will focus on symptom assessment, specifically of depression, in palliative care, on the differences in frequency and timing of specialist palliative care between cancer types and the reasons for non-referral and we will examine the effect of early and systematic integration of palliative care in oncology in Belgium. This dissertation focusses on patients with advanced cancer.

Three aims, each with specific research questions, guide this dissertation:

The **first aim** is to explore the challenges of palliative care in oncology with regards to symptom management and referral practices to specialist palliative care. The following research questions will be answered:

1) What is the prevalence of symptoms of major depression and what are associated factors in a large sample of cancer patients enrolled in a palliative care program?.
2) Are there differences between cancer types in the use and timing of referral to specialized palliative care services and what are the reasons for non-referral?

The **second aim** is to describe the study protocol of a randomized controlled trial of early and systematic integration of palliative care in oncology in the Belgian health care setting.

The **third aim** is to examine the effect of early and systematic integration of palliative care in oncology. The following research questions will be answered:

3) What is the effect of early and systematic integration of palliative care in oncology for patients with advanced cancer soon after diagnosis?
4) What is the effect of early and systematic integration of palliative care in oncology on informal carers of patients with advanced cancer?
5) What is the effect of early and systematic integration of palliative care in oncology on end-of-life care and quality of life near death?

1.4. Methods

To answer the research questions of this dissertation, three different data collections are used. We used a prospective cohort study to assess the prevalence and variability of a positive screening for symptoms of major depression in cancer patients enrolled in a palliative care program (Chapter 2). To address the objective regarding differences in use and timing of specialized palliative care in different cancer types, we used a post-mortem survey investigating end-of-life care, including specialist palliative care, using a representative sample of official death certificates in Flanders (Chapter 3). To address the effects of early and systematic integration of palliative care in oncology, we conducted a randomized controlled trial in the Ghent University Hospital (Chapter 4 to 7). The methods are explained in the following paragraphs.

1.4.1. Study 1: An international prospective cohort study among cancer patients enrolled in a palliative care program.

We used data from the European Palliative Care Cancer Symptom (EPCCS) study. This is an international, multi-center, prospective data collection in a population of palliative care cancer patients. The EPCCS study was conducted in 30 centers in 12 countries between April 2011 and October 2013: Australia, Belgium, Canada, Denmark, Georgia, Germany, Italy, Norway, Portugal, Spain, Switzerland, and UK. The study consisted of a single web-based survey on palliative care organization and approximately monthly assessments and symptom reports of patients enrolled at each unit[45–47].

All patients underwent a first clinical assessment (baseline) and then at each monthly encounter for up to 6 months, death or study withdrawal. At baseline, data were obtained on demographics, such as time from cancer diagnosis, diagnosed comorbidities, etc. At each study assessment, data were collected on clinical characteristics and medication, severity of symptoms and health related quality of life. Depression was assessed with two items on anhedonia and depressed mood (the main items within the DSM-5 criteria for

depression) from the Brief Patient Health Questionnaire PHQ9 [48–50]. Date of death was ascertained from each study center 6 months after the last study inclusion[45,47].

Ethical consideration

The study was performed according to the rules of the Helsinki declaration and was registered in the Clin Trial Gov database (No. NCT01362816). Ethical approval was obtained at each site before study start. All participants provided written consent. The trial office in Norway received anonymized data only.

1.4.2. Study 2: A mortality follow-back study among physicians of patients who died of cancer.

Data of the death certificate study was used for this quantitative mortality follow-back design, looking backwards from death[51–53]. The data used in this dissertation were collected within Flanders, Belgium, in the first half of 2013.

A stratified random sample of deaths was drawn weekly at the Flemish Agency for Care and Health, the central administration authority for processing death certificates. One third of all cancer deaths from January 1st until June 30th 2013 of Belgian residents aged one year or older were sampled. Stratification was disproportionally based on the likelihood that an end-of-life care decision (ELD) had been made, as determined by the cause of death. Questionnaires were mailed to the physicians who signed the death certificates. Within the questionnaire physicians were asked if one or more of the existing types of specialised palliative care in Belgium had been involved in the care of the deceased patient. The response rate was 60.6%[54].

Ethical consideration

To guarantee absolute anonymity, a lawyer served as an intermediary between responding physicians, researchers and the Flemish Agency for Care and Health, ensuring that completed questionnaires could never be linked to a particular patient or physician. The mailing and anonymity procedure were approved by the Ethical Review Board of the University Hospital of the Vrije Universiteit Brussel, the Belgian National Disciplinary Board of Physicians, and the Belgian Privacy Commission.

1.4.3. Study 3: A randomized controlled trial of the effect of early palliative care in oncology

We conducted a non-blinded randomized controlled trial to evaluate early and systematic integration of palliative care in usual oncology care, as compared to usual oncology care alone. From April 29, 2013 to February 29, 2016, we enrolled 186 patients with advanced cancer with a life expectancy of approximately one year. Patients were recruited from the Medical Oncology department, Thoracic Oncology department, or Digestive Oncology department of the Ghent University Hospital in Flanders, Belgium. Upon enrolment,

patients were asked to identify an informal carer who would be invited to participate in the study. One hundred fifteen informal carers agreed to participate in the trial.

Patients and their carers were randomly assigned in a 1:1 ratio, stratified by treating department, to either systematic early integration of palliative care (intervention group) or to usual oncology care (control group). Patients assigned to the intervention group met with a palliative care nurse within 3 weeks after enrolment. Consultations were organized monthly until death and organized at the time of a planned hospital oncology consult. The palliative care physician visited patients mostly upon request of the palliative care nurse. In usual oncology care, the members of the palliative care team are only involved in the treatment trajectory of cancer patients on demand, often late in the disease trajectory: consultations with the palliative care team members are not systematically offered to all oncology patients.

The primary outcome measure is quality of life measured with the global health/quality of life scale of the the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C30[55,56]). Secondary outcomes are quality of life measured with the McGill Quality of Life Questionnaire[57,58], mood with the Hospital Anxiety and Depression Scale (HADS[59,60]) and the Patient Health Questionnaire 9[49,61] and illness understanding (measured by the forward-backward translation of a questionnaire developed by the researchers of the previously mentioned landmark study of early palliative care[25]). Other secondary objectives are related to the informal carers: outcomes were collected with self-assessment instruments on quality of life (Health Survey Short Form 36v2[62–65]), mood (HADS[59,60]), illness understanding and satisfaction with care (FAMCARE[66,67]).We also collected data on health care use from the medical records of the patients, including use of chemotherapy, number of hospital admissions, number of visits by the psychologist or social worker and date and location of death.

Ethical Considerations

The Ethical Committee of the University Hospital Ghent approved the study protocol, oncologists described the study to patients and all participants provided written informed consent.

1.5. Dissertation outline

Following this introduction, Chapter 2-7 of this dissertation are based on articles which have been published, accepted or submitted for publication.

This dissertation consist of three parts, consisting of different chapters that answer specific research questions and aims:

Part II of this thesis focusses on the challenges of palliative care in oncology with regards to symptom management and referral practices to specialist palliative care. This parts aim is to answer research question one and two of this dissertation.

In Part III we describe the need for and the design of a randomized controlled trial of early and systematic integration of palliative care in oncology in the Belgian health care setting.

In Part IV, we examine the effects of early and systematic integration of palliative care in oncology compared to usual care. This part aims to answer research questions three to six of this thesis.

The final Chapter of this dissertation (PART V) consists of the main findings of each research question, reflections on its strengths and limitations, discussion of the findings in relation to the state of affairs within the existing palliative care research and the implications of the findings for practice, policy and future research.

References

1 Fisch MJ, Lee JW, Weiss M, *et al.* Prospective, observational study of pain and analgesic prescribing in medical oncology outpatients with breast, colorectal, lung, or prostate cancer. *J Clin Oncol* 2012; **30**: 1980–8.

2 Teunissen SCCM, Wesker W, Kruitwagen C, de Haes HCJM, Voest EE, de Graeff A. Symptom Prevalence in Patients with Incurable Cancer: A Systematic Review. J. Pain Symptom Manage. 2007; **34**: 94–104.

3 Mohan A, Singh P, Singh S, *et al.* Quality of life in lung cancer patients: impact of baseline clinical profile and respiratory status. *Eur J Cancer Care (Engl)* 2007; **16**: 268–76.

4 Laugsand EA, Kaasa S, de Conno F, Hanks G, Klepstad P, of the EAPC [Collective Name]. Intensity and treatment of symptoms in 3,030 palliative care patients: a cross-sectional survey of the EAPC Research Network. *J Opioid Manag* 2009; **5**: 11–21.

5 Meuser T, Pietruck C, Radbruch L, Stute P, Lehmann KA. Symptoms during cancer pain treatment following WHO-guidelines: A longitudinal follow-up study of symptom prevalence, severity and etiology. Pain. 2001; **93**: 247–57.

6 Cleeland CS, Zhao F, Chang VT, *et al.* The symptom burden of cancer: Evidence for a core set of cancer-related and treatment-related symptoms from the Eastern Cooperative Oncology Group Symptom Outcomes and Practice Patterns study. *Cancer* 2013; **119**: 4333–40.

7 Laugsand E a, Sprangers M a G, Bjordal K, Skorpen F, Kaasa S, Klepstad P. Health care providers underestimate symptom intensities of cancer patients: a multicenter European study. *Health Qual Life Outcomes* 2010; **8**: 104.

8 Greaves J, Glare P, Kristjanson LJ, Stockler M, Tattersall MHN. Undertreatment of nausea and other symptoms in hospitalized cancer patients. *Support Care Cancer* 2009; **17**: 461–4.

9 Pargeon L. KImberly, MA H, B. iley J. Barriers to effective cancer pain management: a review of the literature. *J Pain Symptom Manage* 1999; **18**: 358–68.

10 Meier DE, Brawley OW. Palliative care and the quality of life. *J Clin Oncol* 2011; **29**: 2750–2.

11 Bauman JR, Temel JS. The Integration of Early Palliative Care With Oncology Care : The Time Has Come for a New Tradition. *J Natl Compr Cancer Netw* 2014; **12**: 1763–71.

12 Greer JA., Jackson VA, Meier DE, Temel JS. Early Integration of Palliative Care Services With Standard Oncology Care for Patients With Advanced Cancer. *CA Cancer J Clin* 2013; **63**: 349–63.

13 Ferris FD, Bruera E, Cherny N, *et al.* Palliative cancer care a decade later: Accomplishments, the need, next steps - from the American Society of Clinical Oncology. *J Clin Oncol* 2009; **27**: 3052–8.

14 World Heath Organization. The solid facts: palliative care. 2004 DOI:9289010916.

15 Gaertner J, Wolf J, Ostgathe C, *et al.* Specifying WHO recommendation: moving toward disease-specific guidelines. *J Palliat Med* 2010; **13**: 1273–6.

16 Pardon K, Vanbutsele G. Palliative Care and Cancer. In: Textbook of Palliative Care. Cham: Springer, 2018. DOI:https://doi.org/10.1007/978-3-319-31738-0_56-1.

17 Beernaert K, Deliens L, Pardon K, *et al.* What Are Physicians' Reasons for Not Referring People with Life-Limiting Illnesses to Specialist Palliative Care Services? A Nationwide Survey. *PLoS One* 2015. DOI:DOI:10.1371/journal.pone.0137251.

18 Cohen J, Smets T, Pardon K, Deliens L. Palliatieve zorg meer dan stervensbegeleiding. Leuven: Lannoo Campus, 2015.

19 World Health Organization. Better Palliative Care for Older People. *World Health* 2004; : 40.

20 Lynn J, Adamson DM. Living Well at the End of Life: Adapting Health Care to Serious Chronic Illness in Old Age. *Rand Heal* 2003; : 1–22.

21 Kavalieratos D, Corbelli J, Zhang D, *et al.* Association Between Palliative Care and Patient and Caregiver Outcomes A Systematic Review and Meta-analysis. *JAMA* 2016; **316**: 2104–14.

22 Haun MW, Estel S, Rücker G, *et al.* Early palliative care for adults with advanced cancer (Review). *Cochrane Database Syst Rev* 2017; : 1–105.

23 Bakitas M, Lyons K, Hegel M, *et al.* The Project ENABLE II Randomized Controlled Trial to Improve Palliative Care for Patients with Advanced Cancer. *J Am Med Assoc* 2009; **302**: 741–9.

24 Bakitas M, Sc DN, Lyons KD, *et al.* The project ENABLE II randomized controlled trial to improve palliative care for rural patients with advanced cancer : Baseline findings , methodological challenges , and solutions. *Palliat Support Care* 2009; **7**: 75–86.

25 Temel JS, Greer J a, Muzikansky A, *et al.* Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010; **363**: 733–42.

26 Zimmermann C, Swami N, Krzyzanowska M, *et al.* Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. *Lancet* 2014; : 1721–30.

27 Follwell M, Burman D, Le LW, *et al.* Phase II study of an outpatient palliative care

intervention in patients with metastatic cancer. 2009 DOI:10.1200/JCO.2008.17.7568.

28 Hui D, Kim S-H, Kwon JH, *et al.* Access to palliative care among patients treated at a comprehensive cancer center. *Oncologist* 2012; **17**: 1574–80.

29 Beernaert K, Cohen J, Deliens L, *et al.* Referral to palliative care in COPD and other chronic diseases: a population-based study. *Respir Med* 2013; **107**: 1731–9.

30 Fadul N, Elsayem A, Palmer JL, Zhang T, Braiteh F, Bruera E. Predictors of access to palliative care services among patients who died at a Comprehensive Cancer Center. *J Palliat Med* 2007; **10**: 1146–52.

31 Leblanc TW, O 'donnell JD, Crowley-Matoka M, *et al.* Perceptions of Palliative Care Among Hematologic Malignancy Specialists: A Mixed-Methods Study. *J Oncol Pract* 2015; **11**: 230–8.

32 Morin L, Aubry R, Frova L, *et al.* Estimating the need for palliative care at the population level: A cross-national study in 12 countries. *Palliat Med* 2017; **31**: 526–36.

33 Walsh D, Donnelly S, Rybicki L. The symptoms of advanced cancer: relationship to age, gender, and performance status in 1,000 patients. *Support Care Cancer* 2000; **8**: 175–9.

34 Moran SMC, El-Jawahri A, Pirl WF, *et al.* Symptom burden in hospitalized patients with advanced cancer. *J Clin Oncol* 2015; **33**. http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L72190011%0Ahttp://meeting.ascopubs.org/cgi/content/abstract/33/29_suppl/100?sid=36bea993-e936-4b84-ae33-805ddb8a874f%0Ahttp://sfx.library.uu.nl/utrecht?sid=EMBASE&issn=0732183X&id=d.

35 Teunissen SCCM, Wesker W, Kruitwagen C, de Haes HCJM, Voest EE, de Graeff A. Symptom Prevalence in Patients with Incurable Cancer: A Systematic Review. *J Pain Symptom Manage* 2007; **34**: 94–104.

36 Paice JA. Assessment of symptom clusters in people with cancer. J. Natl. Cancer Inst. Monogr. 2004; : 98–102.

37 Yennurajalingam S, Urbauer DL, Casper KLB, *et al.* Impact of a palliative care consultation team on cancer-related symptoms in advanced cancer patients referred to an outpatient supportive care clinic. *J Pain Symptom Manage* 2011; **41**: 49–56.

38 Fadul NA, Osta E, Dalal S, Poulter VA, Bruera E. Comparison of Symptom Burden among Patients Referred to Palliative Care with Hematologic Malignancies versus those with Solid Tumors. *J Palliat Med* 2008; **11**: 422–7.

39 Strömgren AS, Sjogren P, Goldschmidt D, Petersen MA, Pedersen L, Groenvold M.

Symptom priority and course of symptomatology in specialized palliative care. *J Pain Symptom Manage* 2006; **31**: 199–206.

40 Lloyd-Williams M, Friedman T, Rudd N. An analysis of the validity of the Hospital Anxiety and Depression scale as a screening tool in patients with advanced metastatic cancer. *J Pain Symptom Manage* 2001; **22**: 990–6.

41 Grotmol KS, Lie HC, Hjermstad MJ, *et al.* Depression - a major contributor to poor quality of life in patients with advanced cancer. *J Pain Symptom Manage* 2017; **54**: 889–97.

42 Hayes RD, Lee W, Rayner L, *et al.* Gender differences in prevalence of depression among patients receiving palliative care: The role of dependency. Palliat. Med. 2012; **26**: 696–702.

43 Hotopf M, Chidgey J, Addington-Hall J, Lan Ly K. Depression in advanced disease: A systematic review part 1. Prevalence and case finding. *Palliat Med* 2002; **16**: 81–97.

44 Smith TJ, Temin S, Alesi ER, *et al.* American Society of Clinical Oncology provisional clinical opinion: the integration of palliative care into standard oncology care. *J Clin Oncol* 2012; **30**: 880–7.

45 Hjermstad MJ, Aass N, Aielli F, *et al.* Characteristics of the case mix, organisation and delivery in cancer palliative care: a challenge for good-quality research. *BMJ Support Palliat Care* 2016; **0**: 1–12.

46 Paque K, Elseviers M, Vander Stichele R, *et al.* Changes in medication use in a cohort of patients with advanced cancer: The international multicentre prospective European Palliative Care Cancer Symptom study. *Palliat Med* 2018; **32**: 775–85.

47 Ekström M, Johnson MJ, Schiöler L, Kaasa S, Hjermstad MJ, Currow DC. Who experiences higher and increasing breathlessness in advanced cancer? The longitudinal EPCCS Study. *Support Care Cancer* 2016; **24**: 3803–11.

48 Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA* 1999; **282**: 1737–44.

49 Manea L, Gilbody S, McMillan D. Optimal cut-off score for diagnosing depression with the Patient Health Questionnaire (PHQ-9): a meta-analysis. *CMAJ* 2012; **184**: 191–6.

50 Zuithoff NPA, Vergouwe Y, King M, *et al.* The Patient Health Questionnaire-9 for detection of major depressive disorder in primary care: consequences of current thresholds in a crosssectional study. *BMC Fam Pract* 2010; **11**: 98.

51 van der Heide A, Deliens L, Nilstun T, *et al.* End-of-life decision-making in six European

countries:descriptive study. *Lancet* 2003; : 1–6.

52 Deliens L, Mortier F, Bilsen J, *et al.* End-of-life decisions in medical practice in Flanders, Belgium: a nationwide survey. *Lancet* 2000; **356**: 1806–11.

53 Chambaere K, Bilsen J, Cohen J, *et al.* A post-mortem survey on end-of-life decisions using a representative sample of death certificates in Flanders, Belgium: research protocol. *BMC Public Health* 2008; **8**: 299.

54 Chambaere K, Vander Stichele R, Mortier F, Cohen J, Deliens L. Recent trends in euthanasia and other end-of-life practices in Belgium. *N Engl J Med* 2015; **372**: 1179–81.

55 Fayers P, Bottomley A. Quality of life research within the EORTC—the EORTC QLQ-C30. *Eur J Cancer* 2002; **38**: 125–33.

56 King MT. The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30. *Qual Life Res* 1996; **5**: 555–67.

57 Cohen SR, Mount BM, Bruera E, Provost M, Rowe J, Tong K. Validity of the McGill Quality of Life Questionnaire in the palliative care setting: a multi-centre Canadian study demonstrating the importance of the existential domain. *Palliat Med* 1997; **11**: 3–20.

58 Robin Cohen S, Mount BM. Living with cancer: 'Good' days and 'Bad' days - What produces them? Can the McGill Quality of Life Questionnaire distinguish between them? *Cancer* 2000; **89**: 1854–65.

59 Snaith R, Zigmond AS. Hospital Anxiety and Depression Scale (HADS): 1983 DOI:10.1186/1744-859X-7-4.

60 Spinhoven P, Ormel J, Sloekers PPA, Kempen GIJM, Speckens AEM, VanHemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychol Med* 1997; **27**: 363–70.

61 Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001; **16**: 606–13.

62 Brazier JE, Harper R, Jones NM, *et al.* Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ* 1992; **305**: 160–4.

63 Razavi D, Gandek B. Testing Dutch and French translations of the SF-36 Health Survey among Belgian angina patients. *J Clin Epidemiol* 1998; **51**: 975–81.

64 Farivar SS, Cunningham WE, Hays RD. Correlated physical and mental health summary scores for the SF-36 and SF-12 Health Survey, V.1. *Health Qual Life Outcomes* 2007; **5**. DOI:10.1186/1477-7525-5-54.

65 Grunfeld E, Coyle D, Whelan T, *et al.* Family caregiver burden: results of a longitudinal study of breast cancer patients and their principal caregivers. *CMAJ* 2004; **170**: 1795–801.

66 Kristjanson LJ. Validity and reliability testing of the famcare scale: Measuring family satisfaction with advanced cancer care. *Soc Sci Med* 1993; **36**: 693–701.

67 Ringdal GI, Jordhøy MS, Kaasa S. Measuring quality of palliative care: Psychometric properties of the FAMCARE Scale. *Qual Life Res* 2003; **12**: 167–76.

PART II

Challenges of specialized palliative care in oncology

Chapter 2:

Prevalence and variability of symptoms of major depression in palliative care cancer patients. The longitudinal European Palliative Care Cancer Symptom study (EPCCS-study).

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Abstract

Background Prevalence in major depression (MD) in palliative care (PC) cancer patients are often examined in small sample sizes, as a clinical structural interview is conducted to assess a diagnosis of MD. Canadian and ASCO guidelines recommend that all cancer patients should be screened for symptoms of depression at periodic times across the trajectory of care with validated measures.

Aim To estimate prevalence and variability over time of symptoms of MD by using the Patient Health Questionnaire-2 (PHQ2) as a screener in a large sample of PC cancer patients and to study associated factors.

Methods Data were collected as part of the longitudinal European Palliative Care Cancer Symptom study, including adults with incurable cancer enrolled in PC, with monthly assessments of medical and self-reported data for ≥ 3 months or until death. The PHQ2 assesses the degree of anhedonia and depressed mood in the past 2 weeks on a 0 (not at all) to 3 scale (nearly every day). Prior results showed high sensitivity (89-96%) in primary care. MD (PHQ2 cut-off score of ≥3) is analyzed using multivariate mixed logistic regression.

Results A total of 1699 patients (mean age 65.8) were eligible for analyses. Main diagnoses were digestive (31%), lung (20%), and breast (17%) cancer. Fifty-two percent of the patients (n=883) reported symtoms of MD at some point. At baseline, 36% of the patients experienced symptoms of MD, this decreased significantly to 17% at month 7 and 14% at month ≥8. Independent predictors were pain, anxiety, lower physical functioning (PF) , lower performance status (PS) and the inverse relationship between PF and MD over time (OR=0.99 [95% CI: 0.99 - 1.00]).

Conclusion In a longitudinal clinical study in PC cancer patients, the prevalence of symptoms of MD are high. Symptoms of MD were negatively associated with time, anxiety, pain and positively associated with PF and PS. Interestingly, there is a gradual but strong decline in a symptoms of MD over time.

Chapter 2: Prevalence and variability of symptoms of depression

Introduction

It is widely recognized that it is important to detect and treat depression in patients with cancer, especially in the palliative stage of the disease which focusses on quality of life[1]. Studies have shown that depression has a significant impact on quality of life[2], adherence of treatment [3] and survival time [4,5] of patients with advanced cancer. High levels of depression have been found in cancer patients across different cancer types and stages[6,7]. A systematic review based on studies that used structured psychiatric interviews shows that the median prevalence of major depression ranged from 5% to 26% with a median of 15%[8]. However, in routine clinical practice depression is often undetected and untreated[9]. Research shows that busy cancer specialists have difficulties in identifying emotional suffering of patients[10,11] and oncologists cite a lack of time to perform the necessary diagnostic work for diagnosing depression[12]. This is why routine screening of all cancer patients of depressive symptoms is recommended as it facilitates identification of patients who may be helped by specific therapeutic interventions.[13]. Several guidelines, such as the Pan-Canadian Guideline on Screening, Assessment and Care Of Psychosocial Distress in Adults with Cancer and the American Society of Clinical Oncology Guideline Adaptation[13], underline the importance of using brief tools for screening of depression to minimize patient burden and maximize use in clinical practice.

Previous studies have examined depressive symptoms in palliative care and found associations with demographical variables such as gender[14,15], physical symptoms such as fatigue, daily pain and dyspnea [12,16] and psychological symptoms such as spirituality, cognitive impairment and psychological well-being[16–18]. However, this research is mostly cross-sectional. Some longitudinal studies have examined the changes of depressive symptoms in advanced cancer patients over time[15,19–21] and found that depressive symptoms were elevated after diagnosis of advanced cancer and near the end of life. However, it was not specified in these studies if patients were receiving specialized palliative care. Recent studies show that specialized palliative care positively influences psychological wellbeing and depression of patients[22–24]. There is, however, to our knowledge, limited evidence about the prevalence and change in prevalence of depression over time in cancer patients that are enrolled in a palliative care program.

The objective of this descriptive longitudinal study is to assess the evolution of prevalence of symptoms of major depression over time in cancer patients enrolled in a palliative care program by means of a validated screening instrument. The second objective is to examine the socio-demographic and clinical characteristics that are associated with symptoms of major depression (MD) and change over time.

Methods

Study design and setting

For the purpose of this study, we used data from the prospective, longitudinal multi-center European Palliative Care Cancer Symptom study (EPCCS study) which was conducted in 30 palliative care centers in 12 countries (10 European countries, Australia, and Canada).The study ran from April 2011 through October 2013. Details of the study and participating centers can be found elsewhere.[25] The study consisted of registrations of medical data and patient-reported data on a monthly basis for a minimum of three months or until death.

Study population

The study aimed to include a large number of patients from different sites, with different cancer diagnoses at various stages of their disease, who were defined as palliative care patients and enrolled in a palliative care program. Cancer centers, regional hospitals and hospices/nursing homes were invited to participate in the study through open invitations via the website, meetings and conferences of the European Association for Palliative Care. Centers had to comply with the following inclusion criteria: a center with both oncology and palliative care service or a palliative care service with easy access to oncology service. The inclusion criterion for patient were: advanced, incurable cancer confirmed through radiological, histological, cytological, or operative evidence; age ≥ 18 years; enrolled in a palliative care program; written informed consent; and eligible for at least one follow-up assessment after inclusion. Exclusion criteria were: receiving anti-cancer treatment with a curative intent, inability to complete the registration due to language problems or severe physical problems, having psychotic disorders or obvious cognitive impairment or inability to come for follow-up visits due to geographical or social reasons[25].

Assessments

The data collection consisted of a case report form (CRF) to be completed by the patients and a CFR to be completed by the health care professionals at each patient encounter, every 4 (3-5) weeks for a minimum of three months, or until death or study withdrawal.

The patient case report form

In the patient CRF we collected data on socio-demographic characteristics (age, sex, marital status, education, and living situation), depression using two items from the Patient Health Questionnaire-9 (PHQ2)[26,27], severity of symptoms using the Edmonton Symptom Assessment System-Revised[28] (ESAS-r) and health related quality of life using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative questionnaire[29] (EORTC QLQ-C15-PAL).

The key variable of interest in this analysis was depression as assessed with the two items on anhedonia and depressed mood from the Brief Patient Health Questionnaire- PHQ9[30] corresponding to the main items in the DSM-5 criteria for depression. It assesses the two gateway symptoms of clinical major depression: 1) mood and 2) lack of interest/pleasure in activities (anhedonia). The stem question is, "Over the last two weeks, how often have you been bothered by any of the following problems?" This is followed by the two symptoms: (1) "Little interest or pleasure in doing things," and (2) "Feeling down, depressed, or hopeless." The answering possibilities on each question are: 0 = not at all, 1 = several days, 2 = more than half of the days, and 3 = nearly every day. A sum score is calculated. A PHQ-2 cut-off score of ≥3 had the best trade-off between sensitivity (83%) and specificity (92%) for symptoms of major depression[27].

The health care provider case report form

The health care provider CRF collected a basic set of medical/clinical patient variables: e.g. current treatment, primary cancer diagnosis (ICD-10), diagnosed comorbidities, current medication, time of diagnosis and stage of disease. Other questionnaires used in the health care provider CRF were: the Karnofsky Performance Status scale (KPS), and 4 of the 20 items of the Mini-Mental State Examination[31] (MMSE) for screening for cognitive impairment. A retrospective recording of date of death was performed in each study center in February 2014, approximately six months after the last study inclusion.

Statistical analysis

A mixed logistic regression (glimmix procedure in SAS v9.4) was applied with symptoms of major depression (dichotomous variable based on *PHQ2* ≥ 3) as outcome variable, a random intercept for *country* and a random intercept and slope for *patient*. In each model, the variable time (in months after baseline) was included and we corrected for two demographical parameters, i.e. age and gender, and a clinical parameter, i.e. the interval between time of diagnosis and baseline measurement.

In a first phase, each predictor was tested separately (in combination with the set of demographical parameters). The coefficients derived from the model may indicate a longitudinal between subject relationship of the outcome variable depression and the predictor variable (this means that e.g. a high score on the outcome variable of a patient at different time points, is associated with high scores on predictor variable at different time points), or a longitudinal within subjects relationship (this means e.g. that an increase in the score on the outcome variable depression over time is associated with an increase in score on the predictor variable within the same individual) or both. To distinguish within- versus between-patient effects, within-subject centering was additionally applied to the time-varying continuous predictors (symptom of anxiety measured by the ESAS-r, the performance status measured by the KPS etc.). For each predictor, we also tested the interaction with time (in months after baseline) allowing to detect associations with *change in symptoms of major depression over time*.

In a second phase, the significant predictors and their interactions with time (in months after baseline) were included in one multiple mixed logistic regression model. Subsequently, backward elimination was applied. First, non-significant interaction terms were eliminated stepwise, followed by the non-significant main effects (the set of demographical parameters was retained in the model), which led to the reported final model.

Ethical approval

Ethical approval from the regional committee for Medical Research Ethics was confirmed upon study start for each site. The study was performed according to the rules of the Helsinki declaration and was registered in the ClinicalTrial.gov database (No. NCT01362816). All patients gave written informed consent before entering the study.

Results

Patient characteristics

Patients who didn't have any score on the PHQ2 screening questionnaire for symptoms of major depression, were excluded (n =40) leaving 1699 palliative care cancer patients for analysis. The mean age of the patients was 65.8 years (SD = 12.4). The distribution men versus women was 50%. Twenty five point eight percent of patients completed college or university education. One fifth (20.5%) lived alone, the rest lived with a partner and/or with children or with others. The patients originated from 12 countries (10 European countries, Australia and Canada).

Most frequent principal cancer diagnoses were cancer of the digestive organs (30.6%), cancer of the respiratory organs (20.2%) and breast cancer (16.8%). The place of care at baseline was the palliative care unit of the hospital for nearly half of the patients (46.1%) and the oncology department of the hospital for one third of patients (35.0%), other patients were taken care of at home, in hospice, in a nursing home or in another hospital department than the oncology department. A total of 41.8% patients received chemotherapy at baseline, 40.2% did not receive treatment; 16.3% took antidepressants for depression and 30.8% sedatives/anxiolytics. One fourth of the patients had a KPS of 70, meaning that one is unable to do normal activity or to do active work, but can take care of themselves; 40% did worse and 35% did better. The mean score on the pain scale of the ESAS-r was 2.13 (SD =2.46) with 0 meaning no pain and 10 worst possible pain (Table 1).

Table 1: Characteristics of palliative care cancer patients at baseline (N=1699)

	N(%)	Mean (SD)	Missing N
Socio-demographic characteristics (source: patient questionnaire)			
Age		65.8 (12.4)	1
Sex			2
Male	853 (50.2)		
Female	844 (49.7)		
Marital status			22
Single	154 (9.2)		
Widowed	244 (14.5)		
Divorced/separated	152 (9.1)		
Married/cohabiting	1127 (67.2)		
Highest completed education			26
≤ 9 years of schooling	545 (32.6)		
10-12 years of schooling	695 (41.5)		
College or university ≤ 4 years	265 (15.8)		
College or university > 4 years	168 (10.0)		
Living situation			15
Alone	345 (20.5)		
With spouse/partner	736 (43.7)		
With spouse/partner and children	374 (22.2)		
With children	116 (6.9)		
With other adult(s)	94 (5.6)		
In an institution	19 (1.1)		
Country			0
Belgium, 1 site (WE)	96 (5.7)		
UK, 4 sites (WE)	134 (7.9)		
Norway, 4 sites (NE)	228 (13.4)		
Denmark, 2 sites (NE)	103 (6.1)		
Italy, 7 sites (SE)	605 (35.6)		
Spain, 4 sites (SE)	233 (13.7)		
Portugal, 1 site (SE)	57 (3.4)		
Switzerland , 2 sites (ME)	67 (3.9)		
Bulgaria, 1 site (EE)	29 (1.7)		
Georgia, 1 site (EE)	19 (1.1)		
Australia, 1 site (AU)	35 (2.1)		
Canada, 2 sites (AM)	93 (5.5)		
Clinical characteristics (source: physician questionnaire)			
Provision of care			46
Inpatient	342 (20.7)		
Day care, outpatient	1014 (61.3)		
Home	297 (18.0)		
Place of care			24
Oncology department	586 (35.0)		
Hospital palliative care unit	773 (46.1)		
Other hospital department	20 (1.2)		
Hospice	131 (7.8)		
Nursing home	11 (0.7)		
Primary care setting/home	154 (9.2)		
Principal cancer diagnosis			11
Cancer of the digestive organs	517 (30.6)		
Cancer of the respiratory organs	341 (20.2)		
Breast cancer	284 (16.8)		
Cancer of the male genital organs	126 (7.5)		
Gynaecological cancer	100 (5.9)		
Urinary cancer	77 (4.6)		
Cancer of the head	58 (3.4)		
Leukaemia's and lymphomas	44 (2.6)		
Malignant connective and soft tissue t.	40 (2.4)		
Other[1]	101 (6.1)		
Disease status			17
Local/locally advanced	273 (16.2)		
Metastatic/disseminated	1409 (83.8)		
			13

Comorbidity (number of additional diagnoses: heart disease, arthritis, liver disease, COPD, and/or other)			
0	676 (40.1)		
1	635 (37.7)		
2	282 (16.7)		
3 or more	93 (5.6)		
Treatment with chemotherapy			11
Yes	705 (41.8)		
No	983 (58.2)		
Treatment with radiotherapy			12
Yes	87 (5.2)		
No	1600 (94.8)		
No treatment			12
Yes	678 (40.2)		
No	1009 (59.8)		
Current medication: opioids			
Yes	986 (59.1)		30
No	683 (40.9)		
Current medication: antidepressants for depression			
Yes	271 (16.3)		37
No	1391 (83.7)		
Current medication: sedatives/anxiolytics			
Yes	513 (30.8)		
No	1152 (69.2)		
Performance status according to KPS[2]			13
100 Normal, no complaints	47 (2.8)		
90 Able to carry on normal activity	177 (10.5)		
80 Normal activity with effort	342 (20.3)		
70 Unable normal activity, cares for self	430 (25.5)		
60 Requires occasional assistance	323 (19.2)		
50 Requires considerable assistance	190 (11.3)		
40 Disabled	131 (7.8)		
30 Severely disabled	35 (2.1)		
20 Very sick,	9 (0.5)		
10 Moribund	2 (0.1)		
0 Dead	0 (0.0)		
Status of survival (within study period)			0
Dead	1029 (60.6)		
Alive	337 (19.8)		
Missing	308 (18.1)		
Dead without date of death	25 (1.5)		
Survival, days from inclusion			672[3]
<30	147 (14.3)		
30-89	295 (28.7)		
90-149	183 (17.8)		
150-180	67 (6.5)		
>180	335 (32.6)		
Clinical characteristics (source: patient questionnaire)			
Physical functioning according to EORTC-QLQ-C15-PAL[4]		64.9 (29.19)	
Pain according to ESAS-r[5]		2.13 (2.46)	
Anxiety according to ESAS-r[5]		2.34 (2.76)	

ABBREVIATIONS: SD, standard deviation; KPS, Karnofsky Performance Scale; PHQ2, Patient Health Questionnaire; EORTC-QLQ-C15-PAL, The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative questionnaire; ESAS-r, Edmonton Symptom Assessment System (revised version); WE, Western Europe; NE, Northern Europe; SE, Southern Europe; ME, Middle Europe; EE, Eastern Europe; AU, Australia; AM, America.

[1] Other: including malignant bone tumours (n=8), skin cancer and malignant melanoma (n=35), tumours of the CNS (n=23), malignant endocrine tumours (n=11), secondary and ill-defined malignant tumours and unspecified sites (n=22), multiple primary cancers (n=2).

[2] Performance status according to KPS: ranging from 100% = normal to 0% = dead. The descriptions of the percentages are partial in the table.

[3] 672 missings: including 25 patients reported death but with no date registered.

[4] Physical functioning according to EORTC-QLQ-C15-PAL, ranging from 0 to 100, higher scores mean better physical functioning

[5] Pain according to ESAS-R, ranging from 0 = no pain to 10 = worst possible pain; anxiety according to ESAS-R, ranging from 0 = no anxiety to 10 worst possible anxiety

Number of registrations

A total of 1051 patients or 61.8% had less than 4 registrations/measurements; the median number of monthly registrations was three, minimum one to maximum 11. Reasons for drop-out (if there were less than 4 registrations) were death (48.4%), disease progression (9.5%), lost to follow up (9.3%) and discharged to another location-(8.2%). During the study period, 62.1% of the patients died; 67.3% of these patients died within 6 months after inclusion.

Prevalence and development of symptoms of major depression

During the study 883 patients or 52.0% reported symptoms of major depression on at least one of the monthly registration points. The percentage of patients that reported symptoms of major depression at baseline was 35.7%. The percentage dropped over time to 17.5% at month 7 and 13.6% at month ≥8 (Table 2). The decrease in percentage of patients with symptoms of major depression over time was statistically significant (Odds ratio [OR] 0.954 (95%CI: 0.929 to 0.979) and remained statistically significant after controlling for other variables associated with symptoms of major depression (see below, Table 3 and 5).

Besides significant variation in the prevalence of symptoms of major depression over time, there was also a significant variation in the individual trajectories: 26.3% of patients changed between baseline and month 1 from being depressed to being not depressed (13.8%) or vice versa (12.5%).

Table 2: Prevalence of symptoms of major depression at baseline and every month since baseline of palliative care cancer patients

Timepoints	N(%)									
	Two gateway symptoms of severe depression: Over the last two weeks, how often have you been bothered by any of the following problems?								Severe depression as screened by the PHQ2 via sum score*	Total
	Little interest or pleasure in doing things				Feeling down, depressed or hopeless?					
	0 = not at all	1= several days	2 = more than half of days	3 = nearly every day	0 = not at all	1= several days	2 = more than half of days	3 = nearly every day		
Baseline	544 (32.6)	593 (35.5)	225 (13.2)	308 (18.1)	547 (32.7)	690 (41.2)	202 (12.1)	235 (14.0)	**594 (35.7)**	1666 (100)
Month 1	355 (29.5)	501 (41.6)	194 (16.1)	155 (9.1)	377 (31.2)	574 (47.5)	142 (11.8)	115 (9.5)	**383 (31.9)**	1199 (100)
Month 2	273 (29.2)	392 (41.9)	158 (16.9)	112 (12.0)	313 (33.5)	421 (45.0)	116 (12.4)	85 (9.1)	**289 (31.2)**	927 (100)
Month 3	194 (30.5)	281 (44.2)	92 (14.5)	69 (10.8)	206 (32.3)	302 (47.3)	81 (12.7)	49 (7.7)	**182 (28.7)**	635 (100)
Month 4	130 (28.8)	232 (51.4)	43 (9.5)	46 (10.2)	144 (32.0)	237 (52.7)	37 (8.2)	32 (7.1)	**99 (22.0)**	450 (100)
Month 5	98 (27.8)	182 (51.7)	42 (11.9)	30 (8.5)	103 (29.3)	190 (54.0)	33 (9.4)	26 (7.4)	**78 (22.2)**	351 (100)
Month 6	59 (23.9)	140 (56.7)	31 (12.6)	17 (6.9)	72 (28.9)	131 (52.6)	31 (12.4)	15 (6.0)	**57 (23.1)**	247 (100)
Month 7	16 (40.0)	17 (42.5)	3 (7.5)	4 (10.0)	23 (56.1)	13 (31.7)	5 (12.2)	0 (0.0)	**7 (17.5)**	40 (100)
Month ≥8	21 (42.0)	24 (48.0)	4 (8.0)	1 (2.0)	19 (43.2)	21 (47.7)	4 (9.0)	0 (0.0)	**6 (13.6)**	44 (100)

* A sum score is calculated. A PHQ-2 cut-off score of ≥3 had the best trade-off between sensitivity and specificity for major depressive disorder (severe depression)

Table 3: Characteristics associated with symptoms of major depression as screened by the PHQ2 in palliative care cancer patients

Patient characteristics		Severe depression Odds ratio	95% CI	P-value
Time (in months since baseline)	(continuous variable)	0.8051347	0.742-0.874	**<0.0001**
Time independent characteristics				
Age	(continuous variable)	1.0134	1.003-1.025	**0.0126**
Sex	Male	1.003	0.7771-1.306	0.9798
	Female (ref)	-	-	-
Marital status	Married/cohabiting	0.945	0.717-1.245	0.686
	Single/widowed/separated (ref)	-	-	-
Education	College or university	0.878	0.642-1.202	0.4183
	12 years of schooling or less (ref)	-	-	-
Living situation	Alone	0.991	0.714-1.377	0.9585
	With other (ref)	-	-	-
Cancer diagnosis at baseline	Cancer of the digestive organs	1.589	0.996 – 2.535	0.505
	Cancer of the head	2.080	0.942 – 4.591	
	Cancer of the male genital organs	1.455	0.754 – 2.806	
	Cancer of the respiratory organs	1.356	0.817 – 2.249	
	Gynaecological cancer	1.618	0.863 – 3.035	
	Leukaemia's and lymphomas	1.762	0.704: 4.412	
	Malignant connective and soft tissue tumours	1.663	0.676 – 4.092	
	Urinary cancer	1.526	0.708; 3.286	
	Others	1.551	0.780; 3.011	
	Breast cancer (ref)		-	
Time dependent characteristics				
Provision of care today	Ambulant (day care, outpatient)	0.295	0.216-0.404	**<.00001**
	Home	0.633	0.428-0.935	**0.0218**
	Inpatient (ref)	-	-	-
Place of care today	Hospital palliative care unit/ hospice	1.192	0.907-1.567	0.208
	Hospital department, nursing home, home (ref)	-	-	-
Metastases of the bone	Yes	0.969	0.741-1.269	0.8213
	No (ref)	-	-	-
N comorbidities (from 0 to 3 or more)	(continuous variable)	1.107	0.962-1.274	0.154
Treatment with chemotherapy	Yes	0.505	0.399-0.639	**<.00001**
	No (ref)	-	-	-
No treatment	Yes	1.793	1.443-2.228	**<.00001**
	No (ref)	-	-	-
Current medication: opioids	No	0.794	0.648-0.973	**0.026**
	Yes (ref)	-	-	-
Current medication: antidepressants for depression	No	0.347	0.262-0.460	**<.00001**
	Yes (ref)	-	-	-
Karnofsky Performance Status (KPS, 100% is normal and 0% is dead)	(continuous variable)	0.935	0.928-0.943	**<.00001**
Pain (ESAS item 1, 0 is no pain and 10 is worst possible pain) OK	(continuous variable)	1.292	1.238-1.348	**<.00001**
Anxiety (ESAS item 8, 0 is no anxiety and 10 is worst possible anxiety)	(continuous variable)	1.521	1.462-1.583	**<.00001**
Physical functioning (high score is healthy level)	(continuous variable)	0.954	0.950-0.959	**<.00001**

Estimated on the basis of a mixed logistic regression model with severe depression (PHQ2 ≥ 3) as outcome variable. In each model, the variable time (in months after baseline) was included and we corrected for a set of demographical parameters: age, gender and the interval between time of diagnosis and baseline measurement

ABBREVIATIONS
CI: confidence interval
ref: reference category

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Factors associated with symptoms of major depression

Table 3 shows the factors that were associated with symptoms of major depression as estimated by a mixed logistic regression model including the variable time (in months after baseline) and adjusted for age, sex and the time between cancer diagnosis and baseline. The variable time was associated with symptoms of depression: patients who were one unit, i.e. one month, further in time, had a 0.805 odds of having symptoms of major depression compared to those who were not one month further in time. Age was the only socio-demographic factor that was associated with symptoms of major depression: older patients had higher odds to have and develop symptoms of depression than younger patients. Sex, marital status, education and living situation (alone or with other) were not associated.

Several clinical characteristics were predictive for symptoms of major depression. Patients who were inpatients had higher odds to report symptoms of MD compared to patients who were in day care, treated at home or outpatients Receiving no treatment and receiving no chemotherapy was also positively associated with symptoms of major depression. Patients who had a lower performance status (measured by the KPS) and a lower level of physical function (measured by the EORTC QLQ-C15-PAL), more pain and more anxiety (measured by the ESAS-R) had also increased odds to report symptoms of major depression.

The associations for the continuous time varying factors KPS, physical functioning, pain and anxiety were significant between patients (cross-sectional differences) and within patients (longitudinal change over time) (Table 4).

Table 4: Time-varying continuous predictors of symptoms of major depression as screened by the PHQ2 in palliative care cancer patients distinguishing within- versus between-patient effects

	Between-patients			Within-patients		
Patient characteristics	**Odds ratio**	**95% CI**	**P-value**	**Odds ratio**	**95% CI**	**P-value**
Karnofsky Performance Status (KPS, 100% is normal and 0% is dead)	0.937	0.926-0.947	**<.00001**	0.934	0.922-0.946	**<.00001**
Pain (ESAS item 1, 0 is no pain and 10 is worst possible pain) OK	1.428	1.326- 1.538	**<.00001**	1.207	1.139 - 1.280	**<.00001**
Anxiety (ESAS item 8, 0 is no anxiety and 10 is worst possible anxiety)	1.788	1.680 - 1.903	**<.00001**	1.329	1.263 - 1.399	**<.00001**
Physical functioning (high score is healthy level)	0.956	0.950-0.962	**<.00001**	0.950	0.943-0.957	**<.00001**

ABBREVIATIONS
CI: confidence interval

Factors associated with changes in symptoms of major depression over time

To test whether there were factors associated with *changes* in symptoms of major depression over time, we tested for each predictor whether there was an interaction effect with time. The interaction of physical functioning with time was statistically significant: the higher the score on physical functioning (high scores meaning good physical functioning), the stronger the decrease in odds for a positive screening for major depression. An OR for the interaction between physical functioning and time of 0.994 (95%CI: 0.991 to 0.997) was estimated. For each one unit increase in physical functioning, the decrease (per month) in odds of reporting symptoms of major depression was 0.6% stronger. There were no significant interactions of other predictors with time.

Final model of severe depression

In the final model, symptoms of major depression remained associated with time with the odds for symptoms of major depression decreasing over time. Symptoms of major depression was also associated with a lower KPS, lower physical functioning, pain and the interaction term physical functioning-time, but was no longer predicted by older age, being an inpatient (Table 5).

Table 5: Final model: characteristics associated with severe depression as screened by the PHQ2 in palliative care cancer patients

		Severe depression		
Patient characteristics		**Odds ratio**	**95% CI**	**P-value**
Time (in months since baseline)	(continuous variable)	0.807	0.738-0.882	**<.00001**
Age	(continuous variable)	0.997	0.986-1.009	0.635
Sex	Male	0.872	0.664-1.146	0.325
	Female (ref)	-	-	-
Karnofsky Performance Status (KPS, 100% is normal and 0% is dead)	(continuous variable)	0.978	0.969-0.988	**<.00001**
Pain (ESAS item 1, 0 is no pain and 10 is worst possible pain)	(continuous variable)	1.175	1.121-1.232	**<.00001**
Physical functioning (high score is healthy level)	(continuous variable)	0.971	0.964-0.977	**<.00001**
Time*physical functioning	(continuous variable)	0.994	0.991-0.997	**0.00031**

Estimated on the basis of multiple mixed logistic regression model with severe depression (PHQ2 $\geq$ 3) as outcome variable. In the model the significant predictors of severe depression and interactions with time were included, after which backward elimination was applied (the set of demographical parameters was retained in the model).
ABBREVIATIONS
CI: confidence interval
ref: reference category

Discussion

This study examines the prevalence of symptoms of major depression in a large group of cancer patients who were enrolled in a palliative care program and were followed up for a long period of time. More than half of the patients reported symptoms of major depression at least at some point during the disease trajectory. The highest percentage of patients was observed at inclusion in the study (36%) and this percentage decreased gradually but strongly to 18% at month 7 and 14% at month eight or more. We also found significant variation in the individual trajectories: one quarter of the patients changed after a month from experiencing symptoms of major depression to not experiencing such symptoms or vice versa. Symptoms of major depression and the evolution of experiencing these symptoms was associated with lower KPS, lower physical functioning, higher pain and higher anxiety, and with the interaction of physical functioning with time. This interaction means that the higher the score in physical functioning of the patient is or becomes, the stronger the odds decrease to experience symptoms of major depression.

This study has several strengths: a large group of patients with incurable cancer in palliative care has been questioned in several centers in different countries in Europe and beyond, using a validated screening questionnaire for major depression[27]. Most of the studies on depression are characterized by small sample sizes and are restricted to one or two centers[20,32]. Moreover, this is one of the few longitudinal studies[15] that has followed patients monthly over a long time. This provides new findings in the field of development and prevalence of symptoms of depression over time and associated predictors. There are also a number of limitations. Firstly, we used a screening questionnaire, the PHQ2, to measure depression, while the golden standard is the clinical psychiatric interview[33]. However, it is difficult in large-scale studies to interview everyone, and the screening questionnaire PHQ2 has a sensitivity of 83% and a specificity of 92% for detecting symptoms of major depression[27]. Secondly, there were no data available on potential important psychological determinants such as history with depression and the extent to which the patients has a supportive social network.

The prevalence of symptoms of major depression in this study, as measured by the PHQ-2, is high. During the follow-up period more than 52% of the advanced cancer patients reported experiencing symptoms of major depression at least once. If we look at the point prevalence, a good comparison is possible with other studies. At inclusion in the study, 35.7% of patients reported symptoms of major depression. At 7 months this was 17.5% and at ≥8 months this was 13.6%. With the exception of time point month ≥8, the percentages found were higher than the 15% median found in the review by Hotopf et al[8], and higher than the pooled prevalence of 14.9% in the review of Mitchell et al[32]. A possible explanation for this difference is that in this study not all advanced cancer patients were included but only those who were in a palliative care program. It is possible that patients who enter in a palliative care program have more problems or symptoms including depressive symptoms than those who are not included in such a program. Moreover, in comparison with many other studies, this study was conducted in a sample with a much larger

population involving different types of centers and countries which might have tempered the selection of patients[25].

This study shows that there is a great variability in the occurrence of symptoms of depression over time. Firstly, although the prevalence rates are high during the disease trajectory, there was a sharp decline in prevalence from month 0 – this is inclusion in the study - to month ≥8. This decline is gradual and without outliers. These findings are in accordance with other studies that show that depressive symptoms are likely to be greater at specified time points, such as at initial diagnosis[34] or during treatment[35], and then decline over time. It is also not contrary to studies that show that there is a curvilinear growth in major depression in the last months of life[15]. In this study, we studied the patients prospectively during the disease process and not retrospectively starting from death.

Secondly, we also see that there is a large variability in symptoms of major depression not only at the level of prevalence rates declining over time but also at the level of the individual trajectories: over a month time, approximately one quarter of patients changed: some of these patients changed from experiencing symptoms of major depression to no longer experiencing these symptoms and other patients changed in the opposite direction. This confirms that major depression is indeed a syndrome or condition that is variable, e.g. due to treatment or changing conditions[36]. This is also an important reason to frequently screen palliative care cancer patients for depressive symptoms.

Factors associated with symptoms of major depression were KPS, physical functioning, pain and fear. This has also been observed in other studies[12,16,37]. This study indicates that the association is not only cross sectional but also longitudinal. It is important, therefore, not only to monitor people that score low on the aforementioned variables but also to pay close attention when scores on these variables significantly drop. However, KPS, physical functioning, pain and fear did not explain all variability in symptoms of major depression: the significant decrease in symptoms of major depression over time remained significant even after controlling for these variables. Presumably, the decline is also due to a coping shift that is taking place, where people adapt to the diagnosis, treatment and other important changes that occur.[15] Related to this, being in a palliative care program can also make an important contribution in diminishing depression: palliative care is a more holistic approach compared to regular oncology with more explicit attention to psychological, social and spiritual problems. Moreover, the presence of palliative care health care professionals provide a larger support network for the patient which in itself is an important protective factor against depression[38].

Conclusion

In summary, it is an encouraging sign that the prevalence of symptoms of major depression decreases over time since this decline might be related to the provision of palliative care which forms a buffer against depression, both directly and indirectly through the treatment of physical and other problems associated with depression. However, patients who are enrolled in a palliative care program still frequently report symptoms of major depression. It is important that all involved health care professionals are paying attention to this condition and that symptoms of depression are frequently screened for, especially since large variability of experiencing symptoms of major depression occur during the disease trajectory of individual patients.

Declaration of interests

We declare no competing interests.

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References

1. Noorani NH, Montagnini M. Recognizing Depression in Palliative Care Patients. *J Palliat Med* 2007;10:458–64.
2. Grotmol KS, Lie HC, Hjermstad MJ, Aass N, Currow D, Kaasa S, Moum TÅ, Pigni A, Loge JH. Depression - a major contributor to poor quality of life in patients with advanced cancer. *J Pain Symptom Manage* 2017;54:889–97.
3. Kennard BD, Stewart SM, Olvera R, Bawdon RE, hAilin AO, Lewis CP, Winick NJ. Nonadherence in adolescent oncology patients: Preliminary data on psychological risk factors and relationships to outcome. *J Clin Psychol Med Settings* 2004;11:31–9.
4. Lloyd-Williams M, Payne S, Reeve J, Dona RK. Thoughts of self-harm and depression as prognostic factors in palliative care patients. *J Affect Disord* 2014;166:324–9.
5. Pinquart M, Duberstein PR. Depression and cancer mortality: A meta-analysis. *Psychol Med* 2010;40:1797–810.
6. Jones JM, Huggins MA, Rydall AC, Rodin GM. Symptomatic distress, hopelessness, and the desire for hastened death in hospitalized cancer patients. *J Psychosom Res* 2003;55:411–8.
7. Brintzenhofe-Szoc KM, Levin TT, Li Y, Kissane DW, Zabora JR. Mixed Anxiety/Depression Symptoms in a Large Cancer Cohort: Prevalence by Cancer Type. *Psychosomatics* 2009;50:383–91.
8. Hotopf M, Chidgey J, Addington-Hall J, Lan Ly K. Depression in advanced disease: A systematic review part 1. Prevalence and case finding. *Palliat Med* 2002;16:81–97.
9. Daly EJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Gaynes BN, Warden D, Morris DW, Luther JF, Farabaugh A, Cook I, Rush AJ. Health-related quality of life in depression: A STAR*D report. *Ann Clin Psychiatry* 2010;22:43–55.
10. Ita D, Keorney M, O'Slorain L. Psychiatric disorder in a palliative care unit. *Palliat Med* 2003;17:212–8.
11. Mitchell AJ. Are one or two simple questions sufficient to detect depression in cancer and palliative care? A Bayesian meta-analysis. *Br J Cancer* 2008;98:1934–43.
12. Rhondali W, Perceau E, Berthiller J, Saltel P, Trillet-Lenoir V, Tredan O, Coulon JP, Bruera E, Filbet M. Frequency of depression among oncology outpatients and association with other symptoms. *Support Care Cancer* 2012;20:2795–802.
13. Andersen BL, DeRubeis RJ, Berman BS, Gruman J, Champion VL, Massie MJ, Holland JC, Partridge AH, Bak K, Somerfield MR, Rowland JH. Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: An American Society of Clinical Oncology guideline adaptation. *J Clin Oncol* 2014;32:1605–19.
14. Hayes RD, Lee W, Rayner L, Price A, Monroe B, Hansford P, Sykes N, Hotopf M. Gender differences in prevalence of depression among patients receiving palliative care: The role of dependency. *Palliat.*

*Med.*2012;26:696–702.

15. Lo C, Zimmermann C, Rydall A, Walsh A, Jones JM, Moore MJ, Shepherd FA, Gagliese L, Rodin G. Longitudinal study of depressive symptoms in patients with metastatic gastrointestinal and lung cancer. *J Clin Oncol* 2010;28:3084–9.
16. Rodin G, Lo C, Mikulincer M, Donner A, Gagliese L, Zimmermann C. Pathways to distress: The multiple determinants of depression, hopelessness, and the desire for hastened death in metastatic cancer patients. *Soc Sci Med* 2009;68:562–9.
17. Rayner L, Lee W, Price A, Monroe B, Sykes N, Hansford P, Higginson IJ, Hotopf M. The clinical epidemiology of depression in palliative care and the predictive value of somatic symptoms: Cross-sectional survey with four-week follow-up. *Palliat Med* 2011;25:229–41.
18. Mystakidou K, Tsilika E, Parpa E, Smyrniotis V, Galanos A, Vlahos L. Beck Depression Inventory: exploring its psychometric properties in a palliative care population of advanced cancer patients. *Eur J Cancer Care (Engl)* 2007;16:244–50.
19. Lichtenthal WG, Ph D, Nilsson M, Zhang B, Elizabeth D, Ph D, Kissane DW, Breitbart W, Holly G, Ph D. Advanced Stage Cancer Patients Increase as Death. 2012;18:50–61.
20. Rabkin JG, McElhiney M, Moran P, Acree M, Folkman S. Depression, distress and positive mood in late-stage cancer: A longitudinal study. *Psychooncology* 2009;18:79–86.
21. Hammerlid E, Ahlner-Elmqvist M, Bjordal K, Biörklund A, Evensen J, Boysen M, Jannert M, Kaasa S, Sullivan M, Westin T. A prospective multicentre study in Sweden and Norway of mental distress and psychiatric morbidity in head and neck cancer patients. *Br J Cancer* 1999;80:766–74.
22. Bakitas M, Sc DN, Lyons KD, Sc D, Hegel MT, Barnett KN, Brokaw FC, Byock IR, G. HJ, Zhongze L, McKinstry E, Seville JL, et al. The project ENABLE II randomized controlled trial to improve palliative care for rural patients with advanced cancer : Baseline findings , methodological challenges , and solutions. *Palliat Support Care* 2009;7:75–86.
23. Temel JS, Greer J a, Muzikansky A, Gallagher ER, Admane S, Jackson V a, Dahlin CM, Blinderman CD, Jacobsen J, Pirl WF, Billings JA, Lynch TJ. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010;363:733–42.
24. Zimmermann C, Swami N, Krzyzanowska M, Hannon B, Leighl N, Oza A, Moore M, Rydall A, Rodin G, Tannock I, Donner A, Lo C. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. *Lancet* 2014;1721–30.
25. Hjermstad MJ, Aass N, Aielli F, Bennett M, Brunelli C, Caraceni A, Cavanna L, Fassbender K, Feio M, Haugen DF, Jakobsen G, Laird B, et al. Characteristics of the case mix, organisation and delivery in cancer palliative care: a challenge for good-quality research. *BMJ Support Palliat Care* 2016;0:1–12.
26. Thekkumpurath P, Walker J, Butcher I, Hodges L, Kleiboer A, O'Connor M, Wall L, Murray G, Kroenke K, Sharpe M. Screening for major depression in cancer outpatients: The diagnostic accuracy of the 9-

item patient health questionnaire. *Cancer* 2011;117:218–27.

27. Kroenke K, Spitzer RL, Williams JBW. The patient health questionnaire-2: Validity of a two-item depression screener. *Med Care* 2003;41:1284–92.
28. Watanabe SM, Nekolaichuk C, Beaumont C, Johnson L, Myers J, Strasser F. A multicenter study comparing two numerical versions of the Edmonton symptom assessment system in palliative care patients. *J Pain Symptom Manage* 2011;41:456–68.
29. Groenvold M, Petersen MA, Aaronson NK, Arraras JI, Blazeby JM, Bottomley A, Fayers PM, De Graeff A, Hammerlid E, Kaasa S, Sprangers MAG, Bjorner JB. The development of the EORTC QLQ-C15-PAL: A shortened questionnaire for cancer patients in palliative care. *Eur J Cancer* 2006;42:55–64.
30. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16:606–13.
31. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–98.
32. Mitchell AJ, Chan M, Bhatti H, Halton M, Grassi L, Johansen C, Meader N. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: A meta-analysis of 94 interview-based studies. *Lancet Oncol* 2011;12:160–74.
33. Wilson KG, Graham ID, Viola RA, Chater S, De Faye BJ, Weaver LA, Lachance JA. Structured interview assessment of symptoms and concerns in palliative care. *Can J Psychiatry* 2004;49:350–8.
34. Stommel M, Kurtz ME, Kurtz JC, Given CW, Given BA. A longitudinal analysis of the course of depressive symptomatology in geriatric patients with cancer of the breast, colon, lung, or prostate. *Heal Psychol* 2004;23:564–73.
35. Kelly C, Paleri V, Downs C, Shah R. Deterioration in quality of life and depressive symptoms during radiation therapy for head and neck cancer. *Otolaryngol - Head Neck Surg* 2007;136:108–11.
36. Belmaker RH, Agam G. Major depressive disorder. *N Engl J Med* 2008;358:55–68.
37. Hopwood P, Stephens RJ. Depression in patients with lung cancer: Prevalence and risk factors derived from quality-of-life data. *J Clin Oncol* 2000;18:893–903.
38. De Leeuw J, De Graeff A, Ros W, Hordijk G, Blijham GH, Winnubst J a. Negative and positive influences of social support on depression in patients with head and neck cancer: A prospective study. *Psychooncology.* 2000;9:20–8.

Chapter 3:
Use and timing of referral to specialized palliative care services for people with cancer: a mortality follow-back study among treating physicians.

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Abstract

Background: Referral to specialized palliative care services (SPCS) occurs often late in the illness trajectory but may differ across cancer types. We examined differences between cancer types in the use and timing of referral to specialized palliative care services (SPCS) and in the reasons for non-referral.

Method: We conducted a population-based mortality follow-back survey among physicians who certified a representative sample of deaths in Flanders, Belgium. We focused only on sampled death cases of cancer (n=2392). The questionnaire asked about the use of the existing types of SPCS and the timing of referral to these services.

Results: Response rate was 58% (1394/2392). Patients who died from breast, respiratory, head and neck, genitourinary or gastrointestinal cancer had higher chances of using SPCS compared to hematologic cancer patients. The latter most often received treatment with the aim of life prolongation/curation in the last week of life (24%). The most prevalent reason for non-referral was that regular care sufficiently addressed palliative and supportive care needs (51%). This differed significantly between cancer types ranging from 77,8% for breast cancer and 42.1% for hematologic cancer. A second prevalent reason for not using SPCS was that it was not meaningful (enough) (23.9%), particularly for hematologic malignancies (35,1%) and only in 5.3% for breast cancer.

Conclusion: Differences in referral across different types of cancer were found. Referral is more often delayed or not initiated for patients with hematologic cancer, possibly due to differences in illness trajectory. An influencing reason is that physicians perceive palliative care as not meaningful or not meaningful enough for these patients which may be linked to the uncertainty in the disease trajectory of hematologic malignancies.

Introduction

Cancer patients often suffer from various disease- or treatment-related symptoms that may result in high symptom burden, physical, emotional and spiritual suffering, which reduces quality of life [1,2]. Quality of life is increasingly recognized as an important outcome for cancer patients and studies have demonstrated that it is positively influenced by the early integration of specialized palliative care services (SPCS) in standard oncology care [3–6]. The definition of palliative care (PC) of the World Health Organization (WHO) also states that it should be integrated early in the disease trajectory of patients suffering from life-limiting illnesses alongside disease modifying therapies [7]. Not every patient requires specialized palliative care since palliative care needs may be met by physicians with basic palliative care skills but in cases of complex palliative care problems, referral to specialized palliative care services (SPCS) is needed[8–10]. Advanced cancer is often associated with high and complex symptom burden but research shows low referral to specialized palliative care programs in oncology care [11]. In addition, SPCS are traditionally still initiated very close to death and not early in the disease trajectory [12–14].

Previous research of use and timing of SPCS found that cancer patients were referred 16 days prior to death but perceived cancer patients as a homogeneous group and did not examine differences in referral between cancer types [12,14]. However, different cancer types have distinct symptom clusters and illness trajectories, and physicians have reported that these aspects influenced their past decisions to refer to SPCS [15–19]. In addition, also non patient-related characteristics such as physician and staff's knowledge about palliative care and SPCS influences referral practices, practice specialty even influences patient's survival after referral to SPCS [18]. This suggests that differences in referral and timing of referral might exist between oncology subspecialties and hence cancer types [20].

Some studies looked at the availability of SPCS for patients in cancer types and reported significant differences between cancer types in timing of referral to palliative care [21,22]. However, this evidence is limited to data at an institutional level, not at population level. Information is needed at a population level in order to assess the actual integration of palliative care in oncology care across care settings.

The aim of this population-based retrospective study is to examine whether there are differences between cancer types in the use of SPCS, in the type of service used in particular in the timing of referral to SPCS, and in the reasons for non-referral?

Methods

Death certificate study

We conducted a population-based survey, based on a large and representative sample of death certificates in Flanders, Belgium. The Flemish Agency for Care and Health, the central administration authority for processing death certificates, selected a random sample of deaths in the first half of 2013. For this analysis, we focus only on sampled death cases of malignant cancer (ICD-10 C00-C97). One third of all cancer deaths of Belgian residents aged one year or older were sampled from January 1st until June 30th 2013. This resulted in a sample of 1394 cancer related-deaths.

Within two months of the death, every physician certifying a death certificate in the sample received a questionnaire about the end-of-life care and decision making regarding this case. The physicians were requested to complete the questionnaire consulting the patient's medical file. If the certifying physician was not the treating physician, the questionnaire was to be passed on to the treating physician. A one-page questionnaire was mailed to all non-responding physicians, inquiring about reasons for not participating.

Questionnaire

The questionnaire about end-of-life care and decision making has been repeatedly used in earlier studies [23–25] , the questions regarding palliative care referral, which have been cognitively tested, were added to the questionnaire. The questionnaire first asked whether death had been sudden and totally unexpected. If answered negatively – and hence referral to specialised palliative care services could not be precluded – physicians were asked whether and when they had: (1) initiated specialized palliative care services, (2) what the treatment goal was in the last week of life and (3) what the reasons were for not using SPCS.

1. *Use of specialised palliative care services.* The physician was asked if one or more of the existing types of SPCS in Belgium had been involved in the care of the deceased patient. These services are: multidisciplinary palliative home care teams (team skilled in palliative care who care for the patient and support the caregivers at home), mobile hospital-based palliative care teams (multidisciplinary team that guides palliative care in the different wards of the hospital), inpatient palliative care units (separate wards in the hospital with a multidisciplinary team delivering palliative care) and a palliative care reference person in a nursing home (usually a nurse) trained in and responsible for palliative care. The physician was also asked to indicate the timing of the referral, i.e. the number of days between the first referral to a SPCS and death.

2. *Treatment goal in the last week of life.* The physician was asked to indicate the main treatment goal in the last week of life, the possibilities were life prolongation/curation or comfort/palliation.
3. *Reasons for not using palliative care services.* When none of the SPCS been involved in the end-of-life care of the patient, physicians could mark the reasons why no such services were used: 1) palliative care was not meaningful or not meaningful enough, 2) palliative care was not available, 3) existing care already sufficiently addressed the patient's palliative and supportive needs, 4) there was not enough time to initiate palliative care, 5) in order not to deprive the patient and/or family of hope, 6) the patient did not want it, 7) the family did not want it or 8) another reason (with the request to specify the reason in text). The reasons in this category were afterwards checked by the researchers and allocated to one of the previous categories where possible. Physicians could tick more than one reason for each patient. The possible reasons were selected based on relevant literature about factors hindering the use of palliative care services [17,18,26–29] and on preceding qualitative research on reasons for not using palliative care [30].

Demographic and clinical patient data were obtained from the death certificate and linked anonymously after data collection.

Analysis

The response sample was corrected to be representative of all cancer deaths in the first half of 2013 in terms of age, sex, marital status, province of death, cause of death and place of death (adjustments only needed for place of death). After this weighting procedure there were no significant differences between response sample and all deaths on any of these variables. For this analysis, we considered only non-sudden deaths. Pearson chi square tests analyses were performed for patient and treatment characteristics according to cancer types. For referral to SPCS and reasons for not referring to SPCS non-sudden deaths were considered due to the format of the questionnaire. We also performed a multivariable logistic regression to look at differences between cancer types in SPCS referral and to explore characteristics of cancer patients that are independently related to the use of specialised palliative care services. The non-parametric Kruskal-Wallis test was calculated to test for differences in timing of referral between cancer types. All calculations were made using the in SPSS version 23.0 (SPSS, Inc., Chicago, IL).

Anonymity and ethical considerations

To guarantee absolute anonymity for participating physicians, a lawyer served as an intermediary between responding physicians, researchers and the Flemish Agency for Care and Health, ensuring that completed questionnaires could never be linked to a particular patient or physician. After data collection a one-page questionnaire was mailed to all non-responding physicians, inquiring about reasons for not participating. The mailing and anonymity procedure were approved by the Ethical Review Board of the University Hospital of the Vrije Universiteit Brussel, the Belgian National Disciplinary Board of Physicians, and the Belgian Privacy Commission.

Results

Questionnaires were returned for 1,394 of 2,669 cancer deaths. Non-response questionnaires revealed that responding was impossible in 277 cases, for example because the physician did not have access to the medical file or the patient could not be identified. Therefore, the response rate was 58.3% (1,394 of 2,392 cases).

Case Characteristics

Patients dying from different cancer types (breast, respiratory, gastrointestinal, genitourinary, head and neck, hematologic or other cancers) differed significantly in terms of distribution for sex, age, living situation and marital status (Table 1).

Use of specialized palliative care services

The use of specialized palliative care services differed between cancer types (p=0.007). People who died from head and neck cancer used specialized palliative care services the most (86.3%), in all other cancer patients over 73% get access to SPCS, except for people who died from hematologic cancer with 56.4%.

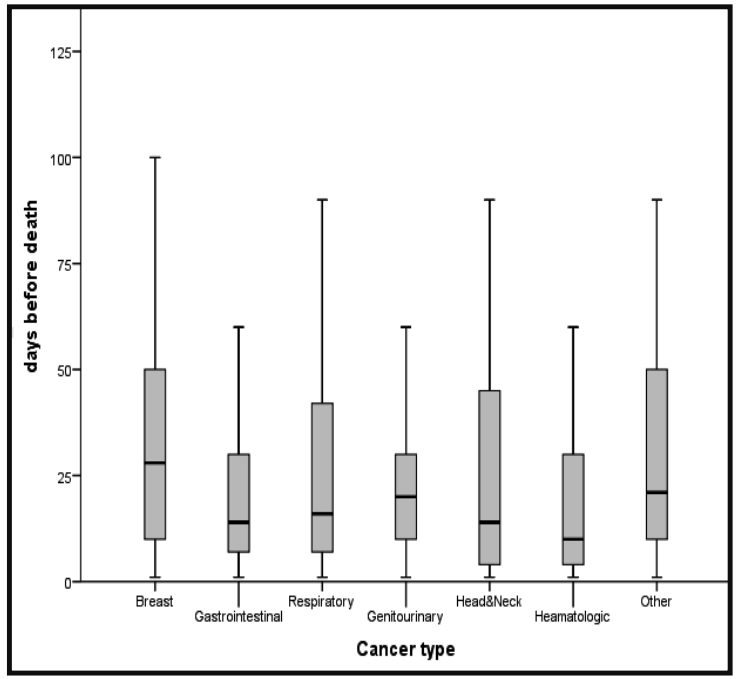
The median timing of referral before death was highest in breast cancer patients (29 days) and lowest in hematologic cancer patients (10 days) (Figure 1). Figure 1 shows an important variation in timing of referral to specialized palliative care services in the groups of patients who died from breast cancer, respiratory cancer or head and neck cancer, while for gastrointestinal, genitourinary and hematologic cancer this within-group variation was less. However, these differences between cancer types were not statistically significant (Table 2). The treatment goal in the last week of life differed between cancer types (p= > 0.001). Hematologic cancer patients most often received treatment aimed at life prolongation or curation in the last week of life (44.1%), for the other cancer types this varied from 23% to 33%.

Table 1. Patient characteristics of all non-sudden cancer deaths according to cancer types.

	All cancer deaths (n=1079)	Breast (n=90)	Gastrointestinal (n=317)	Respiratory (n=266)	Genitourinary (n=187)	Head and Neck (n=31)	Hematologic (n=89)	Other (n= 98)	p-value†
Sex									<0.001
Male	57.6	0	59.9	71.1	58.8	77.4	64.0	51.5	
Age at death									<0.001
1-64y	25.1	34.4	21.4	31.1	10.7	58.1	18.2	36.1	
65-79y	41.3	41.1	43.1	46.8	43.9	29.0	29.5	29.9	
≥ 80y	33.6	24.4	35.5	22.1	45.5	12.9	52.3	34.0	
Place of death									0.057
Hospital (excl. PCU)	40.5	33.0	40.0	44.3	37.5	35.5	51.7	35.7	
PCU	13.2	22.0	12.4	12.5	12.5	16.1	10.1	13.3	
Home	34.9	28.6	36.2	37.5	34.2	41.9	25.8	36.7	
Care Home	10.7	16.5	10.5	5.7	14.1	6.5	12.4	13.3	
Other	0.7	0.0	1.0	0.0	1.6	0.0	0.0	1.0	
Living Situation									0.039
Alone	*21.5*	*20.2*	*18.5*	*19.7*	*26.1*	*25.8*	*29.2*	*19.6*	
In household with others	*67.5*	*62.9*	*72.7*	*72.7*	*60.3*	*64.5*	*55.1*	*68.0*	
Institution	*11.1*	*16.9*	*9.3*	*7.6*	*13.6*	*9.7*	*15.7*	*12.4*	
Marital status									<0.001
Unmarried	7.1	3.3	7.6	6.8	4.3	16.7	10.0	10.2	
Married	57.3	52.2	59.3	62.4	58.3	53.3	45.6	52.0	
Widowed	26.0	37.8	26.2	16.2	28.9	13.3	38.9	27.6	
Divorced	9.5	6.7	6.9	14.3	8.6	16.7	5.6	10.2	
Other	0.1	0.0	0.0	0.4	0.0	0.0	0.0	0.0	
Attending physician									0.017
Hospital specialist	50.0	50.0	47.8	53.9	47.1	38.7	59.6	47.4	
Family physician	46.6	50.0	46.8	43.8	49.7	48.4	39.3	50.5	
Other	3.3	0.0	5.4	2.2	3.2	12.9	1.1	2.1	

Percentages are column percentages. †Pearson $\chi 2$ test testing for differences between the types of cancer: breast, respiratory, colorectal, genitourinary and other. * Other: bone & articular cartilage -, skin-, eye; brain & central nervous system-, thyroid & endocrine glands-, ill-defined; secondary and unspecified sites and independent multiple sites.

Figure 1: Box plot of timing of referral to palliative care services (days before death) per cancer type,



Outliers are not shown and differ per cancer type: Breast: > 114 days (n=7); Gastrointestinal: > 64 days (n=26); Respiratory: >107 days (n=11); Genitourinary: > 60 days (n=14); Head &Neck: >107 days (n=1); Hematologic: > 65 days (n=5); Other: > 105 (n=5). The whisker plot limits describe the maximum and minimum number of days.

Table 2. Rates, timing of referral to specialist palliative care services and treatment goal in the last week of life; % of non-sudden deaths

	Breast (n=90)	Gastro-intestinal (n=317)	Respiratory (n=266)	Genitourinary (n=187)	Head and Neck (n=31)	Hematologic (n=89)	Other (n= 98)	p-value
Any type of PC	79.5	73.1	75.9	75.6	86.3	56.4	78.4	0.007
Palliative care support at home	30.9	29.3)	235.1	27.8	43.8	20.2	35.1	0.076
Hospital-based palliative care service (excl. Palliative care unit)	32.2	32.5	36.3	31.3	37.2	27.7	23.5	0.503
Palliative care unit	19.7	15.8	14.0	15.2	23.8	12.8	15.0	0.805
Palliative care reference person in a nursing home	13.7	5.7	1.6	9.0	5.0	3.5	9.5	<0.001
Other	3.5	3.4	2.6	5.6	0.0	0.0	1.8	0.172
Median days prior to death*	29	14	19	20	14	10	21	0.173
P25 & P75	10;52	7; 30	7; 47	10;30	4; 45	3; 28	10; 48	
Mean	44	35	39	36	37	31	35	
Treatment goal in the last week								
Life prolongation/curation	25.2	33.4	26.4	29.2)	23.1	41.1	30.2	0.044
Comfort/palliation	74.8	66.6	73.6	70.8	76.9	58.9	69.8	

Percentages are column percentages. Percentages may add up to more than the total percentage of referrals because more than one palliative care service was used in some cases.
*Calculations for only patients with a referral to palliative care services, n=792. Missing values 12.8% (n=101) †Pearson χ^2 test testing for differences in referral between the seven different cancer types.
‡Kruskal-Wallis test testing for differences in time of onset between the seven cancer types, minimum 1, maximum 666

Characteristics associated with using specialized palliative care services

When comparing the use of palliative care services between solid cancer types and hematologic cancer in multivariable logistic regression, and after bringing socio-demographic characteristics into consideration, patients who died from breast, gastrointestinal, respiratory, head and neck, genitourinary cancer and patients dying from other cancers had higher odds of using specialized palliative care services compared to patients dying from hematologic cancer (Table 3).

Table 3: Multivariate odds ratios for referral to specialist palliative care services, according to type of cancer and sociodemographic characteristics for all non-sudden cancer deaths.

	Using SPCS* OR (95% CI) multivariate
Type of Cancer	
Breast	***2.25 (1.06-4.80)***
Gastrointestinal	***2.00 (1-17-3.44)***
Respiratory	***2.29 (1.31-4.02)***
Genitourinary	***2.28 (1.25 -4.15)***
Head & Neck	***4.58 (1.34-15.65)***
Hematologic	Ref Cat
Other	**2.60 (1.28-5.27)**
Living situation	
Alone	*1.22 (0.80-1.85)*
In household with other	Ref Cat
Institution	*0.72 (0.46-1.11)*
Age	
18-64y	*1.32 (0.86-2.04)*
65-79 y	**1.46 (1.01-2.10)**
≥ 80 y	Ref Cat
Sex	
Male	Ref Cat
Female	***1.42 (1.01-1.99)***

Reasons for not using palliative care services

Of the 19% (n=268) of cancer patients who were not referred to SPCS, the physician perceived the regular care as sufficiently addressing the patient's palliative and supportive needs in 51% of the cases (Table 4). This differed significantly between cancer types, ranging from 77.8% in breast cancer (77,8%) to 42.1% in hematologic cancers (42.1%),without taking head and neck cancers into account (n=3). Only 4.6% of patients who died of breast cancer did receive neither palliative care nor regular care which, according to the physician, sufficiently met palliative and supportive care needs. This ranged between 15.1% to 8.7% for all other solid cancer types. Patients with hematologic cancer had the highest percentage (25.2%) (Not shown in table).

Another prevalent reason, differing significantly between cancer types, was that palliative care was not meaningful or not meaningful enough according to the physician (23.9%), particularly in hematologic cancer (35.1%). Interestingly, this reason was only mentioned in 5.3% of breast cancer patients. According to the physicians, not having enough time to refer the patient to palliative care services also occurred frequently (26.4%) but this did not differ significantly between cancer types. In some cases (12.7%) patients refused to be referred to specialized palliative care services which differed significantly between cancer types.

Table 4. Reasons given by physicians for not using specialist palliative care services (PCS) in patients who died of cancer.

	Care sufficient (%)	Not meaningful (%)	Not enough time (%)	Patient did not want (%)	Family did not want (%)	Not available (%)	Not take away hope (%)
All cancer types (n=268)	**51.3**	**23.9**	26.4	**12.7**	5.2	1.1	0.7
Cancer type							
Breast (n=19)	**77.8**	**5.3**	16.7	**10.5**	0.0	0.0	0.0
Gastrointestinal (n=83)	**44.0**	**25.3**	27.7	**15.7**	3.6	2.4	0.0
Respiratory (n=62)	**52.4**	**22.6**	23.8	**15.6**	11.1	0.0	1.6
Genitourinary (n=45)	**64.3**	**13.3**	21.4	**4.8**	7.0	2.3	2.2
Head and Neck (n=3)	**0.0**	**33.3**	0.0	**66.7**	0.0	0.0	0.0
Hematologic(n=37)	**42.1**	**35.1**	32.4	**10.5**	0.0	0.0	0.0
Other (n=19)	**52.6**	**42.1**	42.1	**5.3**	5.0	0.0	0.0

Full response answers which physicians could indicate as a reason for not using palliative care services were respectively: the care already sufficiently addressed the patient's palliative and supportive needs; palliative care was not meaningful or not meaningful enough; there was not enough time to initiate palliative care; patient did not want it; family did not want it; palliative care was not available; to not take away the hope of the patient and/or the family.
Abbreviations: PCS= palliative care services.
Percentages are row percentages. Percentages may add up to more than 100 because more than one reason could be indicated in some cases.
*Bivariate Pearson χ^2 test testing for differences in between cancer types. Bold denotes significant at $p<.05$.

Discussion

Our study found that an important proportion of Flemish cancer patients who died non-suddenly in 2013 were referred to specialized palliative care services, varying from 56% for hematologic cancer to 75% for breast cancer. However, this still occurs late in the disease trajectory and referral rates are not equal for patients dying from various cancer types. The most important differences occur between patients with solid tumors and patients dying from hematologic malignancy. Patients with hematologic cancer have smaller chances of referral to any SPCS compared to all other solid cancers, even after controlling for patient characteristics. We also found that they most often received life prolongation or curation in the last week of life. Reasons for non-referral to SPCS also differed between cancer types. The most indicated reasons were that 1) the care received already sufficiently addressed the patient's palliative care needs, 2) there was not enough time and that 3) palliative care was not meaningful or not meaningful enough.

This population-based study constitutes a large representative sample of cancer deaths in Flanders and has an appropriate design to evaluate the referral or non-referral to specialized palliative care services of deceased cancer patients. This study is not limited with regard to care setting or sample size. Furthermore, because of the nationwide scope of this study, our results allow for international comparative research. A shortcoming of this study is the one- to two-month interval between death of the patient and the sending of the questionnaire which might result in recall bias for some cases [24,31,32]. Additionally, since the physician signing the death certificate is occasionally not the patient's treating physician, he/she might not always have knowledge about the specific palliative care services provided, resulting in a possible underestimation of the use of specific specialized palliative care services such as the use of multidisciplinary palliative home care teams. Our study also focuses only on formal care of SPCS, the palliative care approach provided by other health care provisional is neglected. Last, the reasons for not using palliative care only include aspects related to treatment options and are based on the physician's perspectives. Perspectives of patients, carers and other professional caregivers is missing.

Our findings show that SPCS are widely available for cancer patients in Belgium which is similar to other countries such as Canada and Australia[33,34], In addition, most of the cancer patients in this study were either referred to one or more of the different services before death or received regular care which sufficiently supported the palliative care needs according to the physician. These are reassuring results indicating that a palliative care approach is not neglected in oncology care and concur with the palliative care model in Belgium which is very much based on specialized palliative care provided by specialized palliative care professionals and less on a generalist palliative care approach [35].

The idea of palliative care integrated early in cancer care has gained momentum in recent years, yet in day-to-day practice in Belgium specialized services are only involved in the final days of life especially compared to other countries. In our study timing of referral to SPCS did not differ significantly between cancer types, but was the longest for breast cancer patients (median of 29 days) and the shortest for patients with hematologic cancers (median of 10 days). This is late compared to other countries such as the United Kingdom (UK) where patients with breast cancer and patients with hematologic cancer were referred 43.5 and 26 days prior to death respectively[36]. In addition, institutional data shows that in the United States, and in Australia cancer patients were referred, respectively 42 days and54 days prior to death [21,37]. This late referral is an important concern since the end-of-life care in Belgium is more hospital centric with high chemotherapy utilization, compared to other countries such as the United States [38]. This raises the important issue whether palliative care professionals in Belgium have enough time to establish comfort care for cancer patients at the end-of-life.

The found discrepancies in use of specialized PC services between hematologic cancer (54%) and solid cancer types (78%) concur with findings from the UK (12% versus 28%) and Canada (25% versus 36%) [39]. An important finding of our study was that 25% of patients suffering from hematologic cancer were not referred to SPCS or did, according to the physician, not receive usual care that sufficiently addressed the palliative care needs while this is only the case for 5% of patients who died of breast cancer and about 12% for patients who died from all other types of cancer. Several reasons might be related to the discrepancies. One suggested reason is that patients suffering from advanced cancer of solid tumors experience higher, more complex and more diverse symptom burden and thus clearer indications of the need for referral to SPCS [21,40]. Another reason is that the illness trajectory for hematologic cancer is less predictable. Hematologic cancer is often characterized by acute exacerbations of the illness followed by highly technical therapies that can continue over many years. This, along with a rapid dying trajectory, results in difficulties in assessing the right time to refer to SPCS [19,41,42]. This rationale concurs which our findings of the treatment goal of hematologic cancer patients in the last week of life, since this was most often aimed at life prolongation or curation compared to solid cancer.

Nonetheless, hematological cancer patients have been shown to have similar symptom control needs to other cancer patients in all phases of the disease and evidence suggests that hematologic cancer patients have similar patterns of physical decline at the end of life [22,43–45]. This suggests that other factors than clinical and treatment characteristics might also play a role in referral to SPCS. Organizational aspects might influence referral practices since transfusion of blood products might benefit the quality of life of hematologic cancer patients but is often impossible in a palliative setting [46] Also intrapersonal aspects, such as attitudes and perceptions of patients, family and medical staff toward PC may affect referral to SPCS. Interestingly, we found that physicians frequently perceive palliative care as not meaningful or not meaningful enough, particularly so for patients who died from hematologic cancer. Our findings suggest that Belgian hematologic oncologists, compared to solid tumor oncologists, more frequently perceive

palliative care as end-of-life care and perhaps also as antithetical to cancer care [47]. Research shows that hematologists often view treatment goals or disease characteristics in hematology care as incompatible with palliative care and are concerned that referral to SPCS may alarm the patient and family caregiver [48–52].

Our results also point out that palliative care is very well integrated in the usual care for breast cancer patients since 95% of patients who died of breast cancer were referred to SPCS or received usual care that sufficiently addressed the palliative care needs according to the physicians. The mechanism behind these differing results related to cancer type remain unclear. For breast cancer, for example, psychosocial interventions influencing quality of life are well integrated in the regular care which might lead to higher awareness of the benefits of palliative care among professional health carers and patients, resulting in earlier referral to palliative care [53]. Similarly, the perception of professional health carers in hematology may influence patients and families who as a result underestimate the benefits of palliative care and continue to perceive palliative care as terminal care only. Evidence shows that bereaved family members of patients with hematologic cancer felt unprepared for the dying experience and felt unsupported to deal with spiritual pain. This evidence supports the missed opportunity of the benefit of a palliative care approach [43,52].

Conclusion

Despite increasing evidence of the benefit of early integration of palliative care for cancer patients, our study contributes to the awareness that the use of palliative care services in Belgium is high but still occurs late in the disease trajectory. Palliative care is still perceived as terminal care which may lead to unmet palliative care needs of cancer patients and their families, particularly in hematologic malignancy. For these and other cancer patients, further research is needed to test the beneficial effects of early integration of palliative care in oncology care.

References

1 Cleeland CS, Zhao F, Chang VT, *et al.* The symptom burden of cancer: Evidence for a core set of cancer-related and treatment-related symptoms from the Eastern Cooperative Oncology Group Symptom Outcomes and Practice Patterns study. *Cancer* 2013; **119**: 4333–40.

2 Schmidt H, Cleeland CS, Bauer A, Landenberger M, Jahn P. Symptom Burden of Cancer Patients : Validation of the German M . D . Anderson Symptom Inventory : A Cross-Sectional Multicenter Study. *J Pain Symptom Manage* 2014; **49**: 117–25.

3 Temel JS, Greer J a, Muzikansky A, *et al.* Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010; **363**: 733–42.

4 Zimmermann C, Swami N, Krzyzanowska M, *et al.* Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. *Lancet* 2014; : 1721–30.

5 Bakitas M, Lyons K, Hegel M, *et al.* The Project ENABLE II Randomized Controlled Trial to Improve Palliative Care for Patients with Advanced Cancer. *J Am Med Assoc* 2009; **302**: 741–9.

6 Kavalieratos D, Corbelli J, Zhang D, *et al.* Association Between Palliative Care and Patient and Caregiver Outcomes A Systematic Review and Meta-analysis. *JAMA* 2017; **15213**: 2104–14.

7 Sepúlveda C, Marlin A, Yoshida T, Ullrich A. Palliative care: the World Health Organization's global perspective. *J Pain Symptom Manage* 2002; **24**: 91–6.

8 Kaasa S, Jon LH. The Future of Oncology Palliative Care. In: Palliative care in Oncology. Berlin Heidelberg: Springer-Verlag, 2015: 299–308.

9 Quill TE, Abernethy AP. Generalist plus Specialist Palliative Care - Creating a More Sustainable Model. *N Engl J Med* 2013; **368**: 1175–7.

10 Bruera E, Hui D. Integrating Supportive and Palliative Care in the Trajectory of Cancer: Establishing Goals and Models of Care. *J Clin Oncol* 2010; **28**: 4013–7.

11 Hui D, Elsayem A, De la Cruz M, *et al.* Availability and integration of palliative care at US cancer centers. *JAMA* 2010; **303**: 1054–61.

12 Beernaert K, Cohen J, Deliens L, *et al.* Referral to palliative care in COPD and other chronic diseases: a population-based study. *Respir Med* 2013; **107**: 1731–9.

13 Rosenwax LK, McNamara BA. Who receives specialist palliative care in Western Australia--and who misses out. *Palliat Med* 2006; **20**: 439–45.

14 Beernaert K, Deliens L, Pardon K, *et al.* What Are Physicians' Reasons for Not Referring People with Life-Limiting Illnesses to Specialist Palliative Care Services? A Nationwide Survey. *PLoS One* 2015. DOI:DOI:10.1371/journal.pone.0137251.

15 Cheung WY, Le LW, Zimmermann C. Symptom clusters in patients with advanced cancers. *Support Care Cancer* 2009; **17**: 1223–30.

16 Ansell P, Howell D, Garry A, *et al.* What determines referral of UK patients with haematological malignancies to palliative care services? An exploratory study using hospital records. *Palliat Med*

2007; **21**: 487–92.

17 Johnson C, Paul C, Girgis A, Adams J, Currow DC. Australian general practitioners' and oncology specialists' perceptions of barriers and facilitators of access to specialist palliative care services. *J Palliat Med* 2011; **14**: 429–35.

18 Love a W, Liversage LM. Barriers to accessing palliative care: A review of the literature. *Prog Palliat Care* 2014; **22**: 9–19.

19 Manitta VJ, Philip JAM, Cole-Sinclair MF. Palliative Care Review Palliative Care and the Hemato-Oncological Patient: Can We Live Together? A Review of the Literature. *J Palliat Med* 2010; **13**: 1021–5.

20 Lamont EB, Christakis NA. Physician factors in the timing of cancer patient referral to hospice palliative care. *Cancer* 2002; **94**: 2733–7.

21 Hui D, Kim S-H, Kwon JH, *et al.* Access to palliative care among patients treated at a comprehensive cancer center. *Oncologist* 2012; **17**: 1574–80.

22 Fadul N, Elsayem A, Palmer JL, Zhang T, Braiteh F, Bruera E. Predictors of access to palliative care services among patients who died at a Comprehensive Cancer Center. *J Palliat Med* 2007; **10**: 1146–52.

23 Bilsen J, Cohen J, Chambaere K, *et al.* Medical End-of-Life Practices under the Euthanasia Law in Belgium. *N Engl J Med* 2009; **361**: 1120–1.

24 Deliens L, Mortier F, Bilsen J, *et al.* End-of-life decisions in medical practice in Flanders, Belgium: a nationwide survey. *Lancet* 2000; **356**: 1806–11.

25 Chambaere K, Vander Stichele R, Mortier F, Cohen J, Deliens L. Recent trends in euthanasia and other end-of-life practices in Belgium. *N Engl J Med* 2015; **372**: 1179–81.

26 Ahmed N, Bestall JC, Ahmedzai SH, Payne SA, Clark D, Noble B. Systematic review of the problems and issues of accessing specialist palliative care by patients, carers and health and social care professionals. *Palliat Med* 2004; **18**: 525–42.

27 Casarett D, Van Ness PH, O'Leary JR, Fried TR. Are patient preferences for life-sustaining treatment really a barrier to hospice enrollment for older adults with serious illness? *J Am Geriatr Soc* 2006; **54**: 472–8.

28 Brickner L, Scannell K, Marquet S, Ackerson L. Barriers to hospice care and referrals: survey of physicians' knowledge, attitudes, and perceptions in a health maintenance organization. *J Palliat Med* 2004; **7**: 411–8.

29 Walshe C, Chew-Graham C, Todd C, Caress A. What influences referrals within community palliative care services? A qualitative case study. *Soc Sci Med* 2008; **67**: 137–46.

30 Beernaert K, Deliens L, De Vleminck A, *et al.* Early identification of palliative care needs by family physicians: A qualitative study of barriers and facilitators from the perspective of family physicians, community nurses, and patients. *Palliat Med* 2014; **28**: 480–90.

31 Chambaere K, Bilsen J, Cohen J, *et al.* A post-mortem survey on end-of-life decisions using a representative sample of death certificates in Flanders, Belgium: research protocol. *BMC Public*

Health 2008; **8**: 299.

32 Pardon K, Chambaere K, Roeline H, *et al.* Trends in End-of-Life Decision Making in Patients With and Without Cancer. *J Clin Oncol* 2013; **31**: 1450–9.

33 Burge F, Johnston G, Lawson B, Dewar R, Cummings I. Population-based trends in referral of the elderly to a comprehensive palliative care programme. *Palliiative Med* 2002; : 255–7.

34 Hunt RW, Fazekas B, Luke C, Priest K, Roder D. The coverage of cancer patients by designated palliative services : a population-based study ,. *Palliiative Med* 2002; : 403–10.

35 Federale Evaluatiecel Palliatieve Zorg. Evaluatierapport palliatieve zorg. 2014 http://leif.be/data/Wetgeving/Rapporten/Evaluatierapport_palliatieve_zorg_2014.pdf.

36 Bennett MI, Ziegler L, Allsop M, Daniel S, Hurlow A. What determines duration of palliative care before death for patients with advanced disease? A retrospective cohort study of community and hospital palliative care provision in a large UK city. *BMJ Open* 2016; **6**: 1–6.

37 Good PD, Cavenagh J, Ravenscroft PJ. Survival after enrollment in an Australian palliative care program. *J Pain Symptom Manage* 2004; **27**: 310–5.

38 Bekelman JE, Halpern SD, Blankart CR, *et al.* Comparison of Site of Death, Health Care Utilization, and Hospital Expenditures for Patients Dying With Cancer in 7 Developed Countries. *JAMA* 2016; **315**: 272–83.

39 Howell DA, Shellens R, Roman E, Garry AC, Patmore R, Howard MR. Haematological malignancy : are patients appropriately referred for specialist palliative and hospice care ? A systematic review and meta-analysis of published data. *Palliiative Med* 2010; **25**: 630–41.

40 Kwon JH, Hui D, Chisholm G, *et al.* Clinical Characteristics of Cancer Patients Referred Early to Supportive and Palliative Care. *J Palliat Med* 2013; **16**: 148–55.

41 McGrath P, Holewa H. Special considerations for haematology patients in relation to end-of-life care: Australian findings. *Eur J Cancer Care (Engl)* 2007; **16**: 164–71.

42 Auret K, Bulsara C, Joske D. Australasian haematologist referral patterns to palliative care: Lack of consensus on when and why. *Intern Med J* 2003; **33**: 566–71.

43 Manitta V, Zordan R, Cole-Sinclair M, Nandurkar H, Philip J. The Symptom Burden of Patients with Hematological Malignancy: A Cross-Sectional Observational Study. *J Pain Symptom Manage* 2011; **42**: 432–42.

44 Fadul NA, Osta E, Dalal S, Poulter VA, Bruera E. Comparison of Symptom Burden among Patients Referred to Palliative Care with Hematologic Malignancies versus those with Solid Tumors. *J Palliat Med* 2008; **11**: 422–7.

45 Leblanc TW, O 'donnell JD, Crowley-Matoka M, *et al.* Perceptions of Palliative Care Among Hematologic Malignancy Specialists: A Mixed-Methods Study. *J Oncol Pract* 2015; **11**: 230–8.

46 Zimmermann C. Palliative care for patients with hematological malignancies : Time for a new model ☪. *Leuk Res* 2016; **48**: 78–9.

47 Hui D, Park M, Liu D, Reddy A, Dalal S, Bruera E. Attitudes and beliefs toward supportive and palliative care referral among hematologic and solid tumor oncology specialists. *Oncologist* 2015;

20: 1–7.

48 Morita T, Chihara S, Kashiwagi T. Family satisfaction with inpatient palliative care in Japan. *Palliat Med* 2002; **16**: 185–93.

49 Costantini M, Toscani F, Gallucci M, *et al.* Terminal cancer patients and timing of referral to palliative care: A Multicenter prospective cohort study. *J Pain Symptom Manage* 1999; **18**: 243–52.

50 Hui D, Kim SH, Roquemore J, Dev R, Chisholm G, Bruera E. Impact of timing and setting of palliative care referral on quality of end-of-life care in cancer patients. *Cancer* 2014; **120**: 1743–9.

51 Bauman JR, Temel JS. The Integration of Early Palliative Care With Oncology Care : The Time Has Come for a New Tradition. *J Natl Compr Cancer Netw* 2014; **12**: 1763–71.

52 McGrath P. Qualitative findings on the experience of end-of-life care for hematological malignancies. *Am J Hosp Palliat Med* 2002; **19**: 103–11.

53 Rehse B, Pukrop R. Effects of psychosocial interventions on quality of life in adult cancer patients: Meta analysis of 37 published controlled outcome studies. *Patient Educ Couns* 2003; **50**: 179–86.

PART III

A randomized controlled trial of early and systematic integration of palliative care in oncology

Chapter 4:

The systematic early integration of palliative care into multidisciplinary oncology care in the hospital setting (IPAC), a randomized controlled trial: the study protocol.

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Abstract

Background: Previous studies in the US and Canada, have shown the positive impact of early palliative care programs for advanced cancer patients on quality of life (QoL) and even survival time. There has been a lack of similar research in Europe. In order to generalize the findings from the US and Canada research on a larger scale, similar studies are needed in different countries with different care settings. The aim of this paper is to describe the research protocol of a randomized controlled trial, situated in Flanders, Belgium, evaluating the effect of systematic early integration of palliative care in standard oncology care.

Methods/Design: A randomized controlled trial will be conducted as follows: 182 patients with advanced cancer will be recruited from the departments of Medical Oncology, Digestive Oncology and Thoracic Oncology of the Ghent University Hospital. The trial will randomize patients to either systematic early integration of palliative care in standard oncology care or standard oncology care alone. Patients and informal caregivers will be asked to fill out questionnaires on QoL, mood, illness understanding and satisfaction with care at baseline, 12 weeks and every six weeks thereafter. Other outcome measures are end-of-life care decisions and overall survival time.

Discussion: This trial will be the first randomized controlled trial in the Belgian health care setting to evaluate the effect of systematic early integration of palliative care for advanced cancer patients. The results will enable us to evaluate whether systematic early integration of palliative care has positive effects on QoL, mood and patient illness-understanding and which components of the intervention contribute to these effects.

Trial registration: Clinicaltrials.gov Identifier: NCT01865396, registered 24th of May, 2013.

Keywords: Palliative care, End-of-Life, Neoplasm, Advanced cancer, Quality of life, Multidisciplinary care, Mood, Informal caregiver, Study protocol

Chapter 4: Early and systematic integration of palliative care

Introduction

Patients with advanced and incurable cancer typically suffer from a multitude of severe symptoms, which often appear to be under-diagnosed. According to a European multicentre study, symptom intensity is underestimated in one in ten patients, with variations between cancer diagnoses[1]. This underestimation can be explained by a lack of expert knowledge in symptom management, limited time to tend to patients and a strong orientation among health care providers towards cure or life prolongation rather than quality of life, leading to lack of therapeutic pertinacity[2]. There is evidence that all these problems can be tackled by early implementation of palliative care programs (PCPs) in standard oncological treatment[3-5].

Results from recent randomized controlled trials (RCTs) have demonstrated a positive impact on quality of life of PCP. One PCP for advanced cancer patients, situated in the US, consisted of a phone-based psycho-educational intervention led by a palliative care advanced practice-nurse. The RCT study of this intervention demonstrated positive effects on quality of life and lower symptom intensity for cancer patients living in a rural setting[6]. Another RCT study, performed in Canada, implemented an intervention that consisted of a palliative care consultation by a palliative care physician and a palliative care nurse with advanced cancer patients with phone-based follow-up and a 24-h on-call service. Positive effects were reported four months after baseline for quality of life, symptom severity and satisfaction with care[7,8]. Considered as a landmark study on integration of palliative care is the RCT study situated in a major university hospital in Boston, US[4,9,10] where the early palliative care intervention consisted of consultations with outpatients with metastatic non-small-cell lung cancer by a physician from the palliative care team shortly after diagnosis of advanced cancer and at least monthly thereafter. Patients in the palliative care group had significantly higher quality of life and a longer median survival of 2.8 months compared with those who received the standard care alone[4,10,11].

These promising results influenced the American Society of Clinical Oncology (ASCO) to support the full integration of palliative care as a routine part of comprehensive cancer care in the United States[12]. So far, all published results are from studies that have been conducted in the US and Canada; no results have been published on studies in Europe. Before it can become part of general clinical practice, this early palliative care approach has to be tested in different centres and most importantly in different countries where standard oncology care and/or palliative care may be different from that in the US or Canada.

In Belgium standard oncology care in the hospital is organised on a multidisciplinary model. At the medical level, specialists from different disciplines work closely with each other in diagnosing and treating the patient. At a paramedical level, many resources are devoted to ensuring psychosocial support for cancer patients; every hospital in Belgium with an oncology department has a psychosocial team available for patients and their

family carers, consisting of a psychologist, a social worker, a dietician and a nurse specialist. Consultations with the professional caregivers of these teams are free of charge and a first consultation is often organized at the start of treatment. Because of government funding, all hospitals in Flanders, Belgium have a small palliative care team (palliative care nurse 0.5 FTE, palliative care physician 0.5 FTE and palliative care psychologist 0.5 FTE for every 500 hospital beds) available for patients who no longer receive curative treatment or care at the hospital. Palliative care teams are not structurally embedded into the psychosocial team for cancer patients but consultations with them are also free of charge. Patients are mostly seen by a palliative care nurse from the palliative care team[13]. Despite the availability and financial accessibility of palliative care teams, palliative care professionals are only involved in the care of about 60 % of patients with advanced cancer and they are often involved late in the disease trajectory of these patients[14], hence a programme which focuses on systematically providing palliative care early in the disease trajectory of advanced cancer patients is an innovative approach for cancer patients in Flanders, Belgium.

The systematic early integration of palliative care (IPaC) study is the first RCT study on early palliative care for advanced cancer patients to be conducted in the Belgian health care setting. The overall aim of the present paper is to describe the IPaC study protocol.

Methods

Study design

This is a phase III randomized controlled trial (RCT) in a hospital setting with advanced cancer patients receiving systematic early integration of palliative care with standard oncology care versus advanced cancer patients receiving standard oncology care alone. Study participants will be randomized in a 1:1 fashion to the intervention arm or standard care arm. Patients will be recruited from the Digestive Oncology, Thoracic Oncology and Medical Oncology departments of the Ghent University Hospital, the second largest hospital in Belgium. These departments have been selected for the trial because almost all cancer patients in the Ghent University Hospital are treated in these departments. Stratification will take place for the treating oncology department (Digestive Oncology, Thoracic Oncology and Medical Oncology) in order to prevent imbalances between groups in factors related to possible differences in standard care[15].

Study participants

One hundred and eighty two patients with advanced cancer will be recruited by the treating oncologists. Table 1 describes the inclusion and exclusion criteria.

Table 1. Inclusion and exclusion criteria for the patient

Inclusion-criteria	1. Patients with a solid tumour treated at the Medical Oncology department, Thoracic Oncology department or Digestive Oncology department of the Ghent University Hospital 2. Patients within 12 weeks of a new diagnosis of illness progression or patients originating from another hospital who are within 12 weeks of receiving first-line treatment 3. Patients with a life expectancy of approximately one year (assessed by the treating oncologist) 4. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2 5. Patients with the ability to read and respond to questions in Dutch.
Exclusion-criteria	1. Patients under 18 years old 2. Patients with impaired cognition 3. Patients with more than one palliative care consultation since the onset of the disease 4. Patients with one palliative care consultation in the six months before inclusion.

Additionally, participants are given the possibility of identifying an important person in their life, either a relative or friend, to be involved in the study as an informal caregiver. The informal caregivers of patients who are randomised to the intervention group may also attend the consultations and hence frequently meet with the palliative care team as opposed to the informal caregivers of the participants in standard care. Table 2 describes the inclusion-criteria for the family carers.

Table 2: Inclusion criteria for the family carer

1. This person should either live with the patient or have in-person contact with him or her at least twice a week.

Data collection

Oncologists will describe the study to the eligible patients with the help of a data manager. The oncologists are asked to use the terms 'palliative care' and 'palliative care team' specifically while explaining the study, in order for the patient to be thoroughly informed and to avoid confusion when they receive the first visit from

the palliative care team. The oncologists will obtain the patient's written informed consent prior to enrolment. Our researchers will inform the informal caregiver of the patients and obtain written informed consent from them. Study participants will be randomized in a 1:1 fashion to the standard care arm or the intervention arm.

The intervention

The intervention, primarily led by the palliative care nurse, will consist of four major components: the palliative care consultation, assessment, referring role and training.

Palliative care consultation

The intervention consists of systematic consultations with the palliative care nurses of the palliative care team of the Ghent University Hospital shortly after diagnosis of advanced cancer or of the progression of the disease. The palliative care team of the Ghent University Hospital consists of three palliative care nurses (2.5FTE), a palliative care psychologist (0.5FTE) and a palliative care physician (0.5FTE). This systematic early integration of palliative care will be in contrast to standard oncology care, where referral to palliative care is only at the request of physicians, nurses or patients and mostly occurs late in the disease trajectory. The participant receiving systematic early palliative care will meet with the palliative care nurses at least once a month and more if needed or requested by the patient. The palliative care physician will support and advise the palliative care nurses and will have at least one consultation every three months with the participant. All consultations will take place at a time when the patient is at the hospital for diagnostic or therapeutic reasons. The content of the palliative care consultations will be based on the holistic approach of palliative care and will focus on illness understanding and illness perception, symptom burden, psychological coping, spiritual coping and medical decision making by the patient and his or her informal caregiver.

Assessment

An interview form (see: Appendix 1) has been developed to aid in the structuring of each consultation and allows for an individual approach with the patient as well as the informal caregiver[4]. The aim of the members of the palliative care team is to comprehensively assess how the patient and informal caregiver present with regard to illness understanding and illness perception, symptom burden, psychological coping, spiritual coping and medical decision-making at every consultation. However, when a participant is not willing to discuss a specific topic, this will be respected. For symptom burden, assessment will not only be performed through personal inquiry based on the time allocation form but also through the use of the Edmonton Symptom Assessment Scale (ESAS)[16]. The different items of the ESAS will be filled out by the patient and will be discussed with the member of the palliative care team. The palliative care nurse or palliative care physician and the patient will systematically consider the previous item scores of the ESAS by using a graph that plots

the evolution of the scores. This will provide an overview of the fluctuation of the symptoms over time[16].The palliative care team will report the amount of time spent on these different topics on the interview form.

Referring role

Because of their holistic approach to care of the patient, the members of the palliative care team will have an important role in reporting problems that arise during the consultation e.g. debilitating side effects of treatment to the oncology team and other health care professionals involved inside and outside the hospital. To encourage this referring role, the intervention will include regular communication between the members of the palliative care team and other professional caregivers 1) through weekly multidisciplinary meetings with the oncology team; 2) through weekly internal meetings with all the other members of the palliative care team and 3) through reporting in the electronic patient file and the palliative care team is required to complete a referral checklist at the end of every consultation [Appendix 2] which includes an assessment of the need to contact other professional caregivers such as members of the oncology team, the psychologist, the general practitioner and the home palliative care services.

Training

Several information sessions will be organized for the members of the palliative care team on specific early cancer treatments and their possible side effects. The senior oncologists of each department will give a presentation with the focus on cancer etiology, cancer treatment (chemotherapy, radiotherapy, etc.), specific symptoms and side effects and an additional information session will be organized by the researchers on the implementation of the intervention, with topics such as the use and interpretation of the ESAS, the use of the interview form and the referral checklist.

Standard care

In addition to medical treatment, all patients with advanced cancer treated in the Ghent University Hospital receive extensive standard paramedical care. (1) A clinical oncology nurse specialist supports the patients throughout their disease trajectory by providing information on treatment and possible side effects and coordinates hospital appointments. This nurse is available during hospital visits and can be telephoned during working hours. (2) An oncology psychologist helps patients and informal caregivers to cope with the psychosocial implications of cancer and cancer treatment and provides further consultations for the patient and/or their family members at the request of the patient. (3) A dietician has a standard introductory consultation with cancer patients diagnosed with oesophageal cancer, stomach cancer, pancreatic cancer and head and neck cancers. All other cancer patients are screened for weight loss during their hospital stay or treatment and whenever significant weight loss is found, the dietician is consulted. (4) The social worker helps

and supports patients and their relatives in dealing with the consequences of the disease and treatment in their everyday life. They make practical arrangements related to the organization of specific assistance at home and they provide information about financing, social security, insurance and transitions to residential care. The social worker attends at the request of the patient, the oncologist or the oncology nurse. (5) In routine clinical practice in the Ghent University Hospital, the members of the palliative care team are not structurally involved in the treatment trajectory of the cancer patient but at the request of the patient or at the discretion of the attending physicians, or a member of the paramedical team in cases of difficult symptom control and issues related to end-of-life care, such as advance directives. This referral mostly occurs late in the treatment trajectory.

Outcome measures

Study objectives

The primary objective of this study is to assess the impact of this intervention's systematic early integration of palliative care on the patient's quality of life. The secondary objectives are (1) to assess the impact on the patient's median survival time, mood and illness understanding, (2) the impact on informal caregivers' quality of life, mood, illness understanding and satisfaction with care during treatment and after the death of the patient and (3) to examine whether systematic early integration of palliative care, alongside hospital treatment and treatment characteristics, influences advance care planning and end-of-life decision-making.

Measurement instruments

The socio-demographic and clinical characteristics of the patient will be collected at baseline by using questionnaires for the patient and the physician and by consulting the medical record.

Patient and informal caregiver questionnaires. Quality of life of the patient will be measured with the use of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C30) and the McGill Quality of Life Questionnaire (MQOL) [17-19]. The MQOL has been selected because it addresses the existential aspects of quality of life as well as the physical, emotional and social aspects of quality of life. A recent review qualified both its content and construct validity as high[20]. The mood of the patient will be measured by two instruments: the Hospital Anxiety and Depression Scale (HADS) and the Patient Health Questionnaire 9 (PHQ-9) [21-24]. Illness-understanding will be measured by a forward-backward translation of the questionnaire developed by the researchers of the previously mentioned study of palliative care for patients with metastatic non-small-cell lung cancer[4].

Data on mood, quality of life, illness understanding and satisfaction with care of the informal caregivers will be obtained by self-assessment instruments: HADS, PHQ-9, the Short Form-36 Health Survey (SF-36) a questionnaire for illness understanding and by the FAMCARE respectively[25]. A forward-backward translated and tested version of the FAMCARE will evaluate the satisfaction with care of the informal caregivers[26]. The surveys filled out by patients and informal caregivers, their frequency and the timing of completion are detailed in Table 3. The patient will complete the baseline questionnaires before randomization and the follow-up questionnaires with regard to quality of life, mood and illness-understanding firstly after 12 weeks and thereafter every six weeks. Change from baseline to 12 weeks after inclusion is chosen because approximately 80 % of patients are expected to be alive at 12 weeks after inclusion[4]. The informal caregivers will complete the baseline questionnaire before randomization and the follow-up questionnaires firstly after 12 weeks and then every six weeks. If the patient dies the informal caregiver is asked to fill out the questionnaire once more 12 weeks after the death.

Oncologist questionnaires In order to collect information on advance care planning and the making of end-of-life decisions (ELDs), the oncologist will be asked to fill out a validated Dutch questionnaire that has been used many times before in nationwide ELD-incidence studies in Flanders, Belgium. In accordance with previous studies, three main categories of ELDs will be considered: the withholding or withdrawal of potentially life-prolonging treatments (non-treatment decisions), the intensified alleviation of symptoms with a possible life-shortening effect and the administration or supply of drugs with the intention of shortening the patient's life (physician-assisted death)[27,28].

Data on outcomes related to treatment characteristics will be collected from the medical records of the patient, including survival time, intensity of chemotherapy, hospital admissions and frequency of contact with a psychologist/dietician/other health care professional. According to the definitions of Temel et al., patients will be classified as having had aggressive care if they meet one of the following criteria: 1) chemotherapy within 14 days of death, 2) no palliative care involvement in the last three months of life, or 3) admission to a palliative care unit three days or less before death[4].

Table 3: Types of patient and informal caregiver questionnaires and frequency and timing of completion

	Week					
	Baseline	12	18	24	…	12 weeks after patient's death
PATIENT FORMS						
EORTC QLQ C30 and MQOL	X	X	X	X	X	
PHQ-9 and HADS	X	X	X	X	X	
Illness-understanding Questionnaire	X	X	X	X	X	
INFORMAL CAREGIVERS FORMS						
General Health SF-36	X	X	X	X	X	X
PHQ-9 and HADS	X	X	X	X	X	X
FAMCARE	X	X	X	X	X	
Illness-understanding Questionnaire	X	X	X	X	X	

Statistical analysis and sample size calculation

To compare baseline characteristics and study outcomes for patients between groups, Fisher's exact tests, chi-square tests and the independent-samples t-test or the non-parametric equivalent Mann–Whitney U will be used. The effect of early palliative care on the primary outcome quality of life will be assessed by multivariate regression analyses adjusting for baseline scores. Survival analysis, i.e. Kaplan-Meier and a Cox proportional hazards model, will be used to examine the effect of systematic early integration of palliative care on the secondary outcome survival from the time of inclusion adjusting for demographic and clinical baseline characteristics. With regard to missing data, we will use the conservative approach of carrying the last observation forward for all missing data.

To detect a significant and meaningful difference in the change of the EORTC QLQ-C30 from baseline to 12 weeks, 118 patients are needed. With the proposed sample size of 59 for the two groups, the study will have a power of 80 % to yield a statistically significant result. This computation assumes a mean score difference of 12 and the common within-group standard deviation is 23.0. A difference of 10 points on the multi-items scales from 0 to 100 is considered meaningful[50,51]. On the basis of the study on early palliative care in advanced lung

cancer patients, it can be expected that approximately 80 % of the study participants will still be alive at 12 weeks after inclusion and drop-out for reasons other than death will amount to 15 %[4]. In other words, an overall drop-out inclusion of a total of 182 patients in the study.

Ethical considerations

Since the participants in the control group will receive extensive medical and paramedical care and will not be refused palliative care at their request, it is deemed that this research design is acceptable. The procedure of inclusion is organized in such manner that all patients will be informed firstly at inclusion by their treating oncologists and secondly by the data manager. The treating oncologist will spend time explaining the aim of palliative care in general and its specific aim within this study. They will provide an information sheet and an informed consent document to the patient. In a second phase, the data manager will have a consultation of a minimum of half an hour with the patient to explain the nature and procedure of the study in depth and to answer any questions participants might have. The participants will then be asked to give written informed consent and will be given a guarantee that: 1) the data will be treated confidentially, 2) the data will be stored anonymously for analysis later on, 3) study participation will be on a voluntary basis and withdrawal will be possible whenever the patient wishes and 4) non-participation or withdrawing from the study will have no influence on the future care of the patient. After providing informed consent, all patients will fill out the baseline questionnaires in the presence of the data manager so they will be able to request help if necessary. They will also be able to discontinue completing the questionnaire at any moment. Moreover, if they appear to be distressed as a result of filling out the questionnaire, psychologists from the oncology departments will be available to provide counselling.

Approval

Approval for this study was given by the Ethical Committee of the Ghent University Hospital, Flanders, Belgium.

Discussion

The IPaC study is the first randomized controlled single centre phase III trial to implement an early palliative care approach in standard oncological care in the hospital setting in Belgium for patients with advanced cancer. Following a baseline assessment, patients and their informal caregivers will be randomized to either the intervention group where systematic early integration of palliative care will be implemented or to the control group where care will be provided as usual. Follow-up measurements allow the detection of

differences in the quality of life, mood and illness understanding between patients in the intervention group and those in the control group.

Our systematic early integration of palliative care intervention is based on the original guidelines of the early palliative care intervention that was examined in the study for non-small lung cell cancer patients but adaptations have been incorporated to fit the specifics of the Belgian health care setting[4]. A first adaptation lies in the fact that the intervention is primarily led by the palliative care team nurses and not by the palliative care physician, due to the organizational structure of hospital-based palliative care in Flanders. The influence of a nurse-led intervention may appear to be less effective than a physician-led intervention but it may be less costly and financially more feasible[5]. A second adaptation is that the palliative care nurse leading the intervention also has a referring role. The medical and paramedical members of the oncology team may be able to fulfill the palliative care needs of the patient adequately but their goal often remains to prolong life. Palliative care embraces a different approach, focusing on the needs and expectations of the patient from a holistic point of view, which may lead to the eliciting of different information from the patient and the palliative care nurses who, in this trial, have an important role in referring this information to the oncology team. This interdisciplinary approach will broaden the view on care. A third adaptation consists of the semi-systematic format of consultations based on an interview form in which the important palliative care topics that have to be discussed and treated are listed. In addition, standard symptom assessment (ESAS) is incorporated to evaluate symptom intensity at each consultation and to provide an overview of the fluctuation of symptoms. Research has shown that most health care professionals agree that use of the ESAS enhances patient care because it helps patients in articulating their symptom issues and aids in following them up[29].

Several limitations exist with regards to the IPaC study. It is a single-centre study in a tertiary hospital setting, which might limit the generalization of the results to other hospitals. On the other hand, the organization of the oncology departments and palliative care team are similar between hospitals in Belgium, having been developed on the basis of the same legislative initiatives. A second limitation is that participants and staff members are not blinded for allocation to the intervention group or control group. It is possible that the treating oncologists and other members of the oncology team are affected by the new approach and will implement the new insights with patients in the control group (crossover effect). However, the oncologists and other health care professionals of the oncology team will be well informed about the goals and design of the study and will be made aware of bias risks. A third limitation concerns the possibility of selection bias, since participants are asked for consent prior to enrollment. Participants more open to end-of-life discussions might be more prone to taking part in the trial than others.

This trial also has several strengths. Firstly, our study protocol consists of a detailed description of standard oncology care, which has a particular focus on providing psychosocial support for cancer patients and their caregivers. Such a description is needed since the organization of standard care has an important influence on this intervention, specifically on the referring role of the palliative care nurses. The inclusion of this explicit description demonstrates a different approach from other early palliative care RCTs. Extensive information has been provided regarding the functioning of the palliative care clinic and the roles of the palliative care clinician in these trials but little information is available concerning the organization of standard oncology care[4,6-8,30-32]. In the US, a broad range of supportive services are offered by a multidisciplinary cohort of oncology health professionals but the availability of these services varies greatly among institutions. Hence, extrapolation of this information to the organization of the standard care of the early palliative care trials situated in the US is not feasible[33]. Secondly, for our primary outcome measure we have selected a questionnaire (EORTC QLQ-C30) on quality of life which is used in clinical trials in Europe and has been studied intensively from the perspective of the clinical significance of scores[34]. One of the challenges of the trial is the recruitment of patients with advanced cancer early in the stage of the disease trajectory. A systematic review of early integration of palliative care in hospitals has shown that staff-specific barriers often occur due to the reluctance of physicians to communicate prognostic information to the patient and family and the perception by staff of PC as 'terminal care' [35]. Clinicians are often concerned that referral to PC will alarm patients and their informal caregivers[5]. Hence, introducing a clinical trial of PC to advanced cancer patients early in their disease trajectory may prove to be difficult. However, with the support of the head oncologist of each department and the disseminating of the results of previous research in early palliative care we expect that the trial will be successfully initiated in the different departments involved.

Conclusion

The IPaC trial is a randomized controlled trial approved by the Ethical Committee that aims to assess whether the quality of life of patients with advanced cancer and their informal caregivers is enhanced by implementing systematic early integration of palliative care in a setting where multidisciplinary cancer care is part of standard oncology care. This trial will add to the evidence about the effectiveness of integrated palliative care programmes for cancer patients. We hope that this study will not only show whether systematic early integration of palliative care is effective for cancer patients in Belgium but will also provide an increased understanding of the contribution of the different components of the systematic early integration of palliative care intervention to their quality of life.

Abbreviations

IPaC: Integration of Palliative Care; US: United Stated; QoL: Quality of Life; PCPs: Palliative Care Programs; RCT: Randomized Controlled Trial; ASCO: American Society of Clinical Oncology; FTE: Full Time Equivalent; ECOG: Eastern Cooperative Oncology Group; ESAS: Edmonton Symptom Assessment Scale; EORTC QLQ C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; MQOL: McGill Quality of Life Questionnaire; HADS: Hospital Anxiety and Depression Scale; PHQ-9: Patient Health Questionnaire 9; SF-36: Short Form-36 Health Survey; ELDs: End-of-Life Decisions.

Competing interest

The authors declare that they have no competing interests.

Authors' contributions

GV is the principal investigator and the guarantor of this work. The conception and design involved all the authors. The study was coordinated by GV, SVB, MDL, KG, VS, KE, KP and LD. GV is responsible for the acquisition of data. This paper was revised, discussed and amended by all the authors who approved the final version of the manuscript.

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References

1. Fisch MJ, Lee JW, Weiss M, Wagner LI, Chang VT, Cella D, et al. Prospective, observational study of pain and analgesic prescribing in medical oncology outpatients with breast, colorectal, lung, or prostate cancer. *J Clin Oncol*. 2012;30:1980–8.
2. Greaves J, Glare P, Kristjanson LJ, Stockler M, Tattersall MHN. Undertreatment of nausea and other symptoms in hospitalized cancer patients. *Support Care Cancer*. 2009 ;17:461–4.
3. Hearn J, Higginson IJ. Outcome measures in palliative care for advanced cancer patients: a review. *J Public Health Med.* 1997; 19: 193–9.
4. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med*. 2010;363(8):733–42.
5. Bauman JR, Temel JS. The Integration of Early Palliative Care With Oncology Care: The Time Has Come for a New Tradition. *J Natl Compr Cancer Netw*.2014;12(12):1763–71.
6. Bakitas M, Lyons K, Hegel M. The Project ENABLE II Randomized Controlled Trial to Improve Palliative Care for Patients with Advanced Cancer. *J Am Med Assoc*. 2009;302(7):741–9.
7. Zimmermann C, Swami N, Krzyzanowska M, Hannon B, Leighl N, Oza A, et al. Early palliative care for patients with advanced cancer: a cluster randomised controlled trial. *Lancet.* 2014; 18 :1721–30.
8. Zimmermann C. Effectiveness of Specialized Palliative Care : A systematic review. *J Am Med Assoc*. 2014;299(14):1698-1709.
9. Temel JS, Greer J, Admane S, Gallagher ER, Jackson V, Lynch TJ, et al. Longitudinal perceptions of prognosis and goals of therapy in patients with metastatic non-small-cell lung cancer: Results of a randomized study of early palliative care. *J Clin Oncol.* 2011;29(17):2319–26.
10. Pirl WF, Greer JA, Traeger L, Jackson V, Lennes IT, Gallagher ER, et al. Depression and survival in metastatic non-small-cell lung cancer: effects of early palliative care. *J Clin Oncol.* 2012;30:1310–5.
11. Greer JA, Pirl WF, Jackson VA, Muzikansky A, Lennes IT, Heist RS. Effect of early palliative care on chemotherapy use and end-of-life care in patients with metastatic non-small-cell lung cancer. *J Clin Oncol*. 2012;30(4):394–400.
12. Smith TJ, Temin S, Alesi ER, Abernethy AP, Balboni TA, Basch EM, et al. American Society of Clinical Oncology provisional clinical opinion: the integration of palliative care into standard oncology care. *J Clin Oncol.* 2012;30(8):880–7.
13. Zorg FEP. Evaluatierapport palliatieve zorg. 2014. Available from: http://www.palliatief.be/accounts/143/attachments/rapporten/rapport_evaluatiecel_palliatieve_zorg_maart_2014_nl.pdf. Accessed 6 May 2015.
14. Beernaert K, Cohen J, Deliens L, Devroey D, Vanthomme K, Pardon K, et al.Referral to palliative care in COPD and other chronic diseases: a population based study. *Respir Med.* 2013;107(11):1731–9.

15. Nichol AD, Bailey M, Cooper DJ. Challenging issues in randomized controlled trials. *Injury*. 2010;41 Suppl 1:S20–3.
16. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. *J Palliat Care.* 1991;7:6–9.
17. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology.*J Natl Cancer Inst*. 1993; 85: 365–76.
18. Cohen SR, Mount BM, Bruera E, Provost M, Rowe J, Tong K. Validity of the McGill Quality of Life Questionnaire in the palliative care setting: a multicenter Canadian study demonstrating the importance of the existential domain. *Palliat Med.* 1997; 11 :3–20.
19. Robin Cohen S, Mount BM. Living with cancer: "Good" days and "Bad" days - What produces them? Can the McGill Quality of Life Questionnaire distinguish between them? *Cancer.* 2000; 89: 1854–65.
20. Albers G, Echteld MA, de Vet HCW, Onwuteaka-Philipsen BD, van der Linden MHM, Deliens L. Evaluation of quality-of-life measures for use in palliative care: a systematic review. *Palliat Med.* 2010;24:17–37.
21. Katon WJ, Simon G, Russo J, Von Korff M, Lin EHB, Ludman E, et al. Quality of depression care in a population-based sample of patients with diabetes and major depression. *Med Care.* 2004;42:1222–9.
22. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67:361–70.
23. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. *Psychol Med.* 1997;27:363–70.
24. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16:606–13.
25. Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ*. 1992;305:160–4.
26. Kristjanson LJ. Validity and reliability testing of the famcare scale: Measuring family satisfaction with advanced cancer care. *Soc Sci Med*. 1993;36:693–701.
27. Chambaere K, Bilsen J, Cohen J, Onwuteaka-Philipsen BD, Mortier F, Deliens L. Physician-assisted deaths under the euthanasia law in Belgium: a population-based survey. *CMAJ.* 2010;182:895–901.
28. Chambaere K, Bilsen J, Cohen J, Onwuteaka-Philipsen BD, Mortier F, Deliens L. Trends in medical end-of-life decision making in Flanders, Belgium 1998-2001-2007. *Med Decis Making.* 2011;31:500–10.
29. . Bainbridge D, Seow H, Sussman J, Pond G, Martelli-Reid L, Herbert C, et al. Multidisciplinary health care professionals' perceptions of the use and utility of a symptom assessment system for oncology patients. *J Oncol Pract*. 2011;7(c):19–23.

30. Yoong J, Park ER, Greer JA, Gallagher ER JVA, Pirl WF. Early palliative care in advanced lung cancer: a qualitative study. *JAMA Intern Med*. 2013;173(4): 283–90.
31. Jacobsen J, Jackson V, Dahlin C, Greer J, Perez-Cruz P, Billings JA. Components of early outpatient palliative care consultation in patients with metastatic nonsmall cell lung cancer. *J Palliat Med*. 2011;14(4):459–64.
32. Back AL, Park ER, Greer JA, Jackson VA, Jacobsen JC, Gallagher ER, et al. Clinician Roles in Early Integrated Palliative Care for Patients with Advanced Cancer. *J Palliat Med*. 2014;17(11):1244–8.
33. Deshields T, Zebrack B, Kennedy V. The state of psychosocial services in cancer care in the United States. *Psychooncology*. 2013;22(February 2012): 699–703
34. Fayers P, Bottomley A. Quality of life research within the EORTC—the EORTC QLQ-C30. *Eur J Cancer*. 2002;38:125–33.
35. Dalgaard KM, Bergenholtz H, Nielsen ME, Timm H. Early integration of palliative care in hospitals: A systematic review on methods, barriers, and outcome. *Palliat Support Care*. 2014;12:1–19.

Appendices

Appendix 1

Interview form **Date of consultation:**_____

Different topics:	**How much of the time have you discussed the topic?**
Illness understanding–Illness perception Undertaken actions for eventual discomfort**:** _____ _____ _____ _____	**…….%**
Symptom management – (use of ESAS) Undertaken actions for eventual discomfort: _____ _____ _____ _____	……%
Dealing with a life-threatening illness- psychological: Undertaken actions for eventual discomfort _____ _____ _____ _____	**……%**
Dealing with a life-threatening illness – spiritual: Undertaken actions for eventual discomfort _____ _____ _____ _____	**……..%**
Support in eventual decision at the end-of-life: Undertaken actions for eventual discomfort _____ _____ _____ _____	**……..%**
Other topics Undertaken actions for eventual discomfort: _____ _____ _____ _____	**……..%**

Appendix 2

Referral Sheet:

Date of consultation:_____

1. Has the patient got any unanswered question regarding his/her treatment and visits to the hospital?

   ☐ **No**
   ☐ **Yes** → Please contact the **reference nurse**: NAME and TELEPHONE NUMBER

2. Has the patient got any severe and untreated symptoms due to the treatment, or specific questions regarding the treatment and medication?

   ☐ **No**
   ☐ **Yes** → Please contact the **treating physician** or **head** of the department: NAME and TELEPHONE NUMBER

3. Has the patient or his/her informal caregiver got any needs regarding specific social matters?

   ☐ **No**
   ☐ **Yes** → Please contact the **social nurse/social worker**: NAME and TELEPHONE NUMBER

4. Has the patient got any needs regarding nutrition?

   ☐ **No**
   ☐ **Yes** → Please contact the **dietician**: NAME and TELEPHONE NUMBER

5. Has the patient or his/ehr family got any care specific needs regarding psychological matters?

   ☐ **No**
   ☐ **Yes** → Please contact the **psychologis**t: NAME and TELEPHONE NUMBER

6. Is there a need to contact any external professional caregivers?

   ☐ **No**
   ☐ **Yes** → the **family physician**
   → the **home care nurse**
   → the **palliative home care team**

PART IV

The effect of early and systematic integration of palliative care in oncology

Chapter 5:
Effect of early and systematic integration of palliative care in patients with advanced cancer: a randomised controlled trial

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Abstract

Background: The benefit of early integration of palliative care into oncological care is suggested to be due to increased psychosocial support. In Belgium, psychosocial care is part of standard oncological care. The aim of this randomized controlled trial is to examine whether early and systematic integration of palliative care alongside standard psychosocial oncological care provides added benefit compared with usual care.

Methods: In this randomised controlled trial, eligible patients were 18 years or older, and had advanced cancer due to a solid tumour, an European Cooperative Oncology Group performance status of 0–2, an estimated life expectancy of 12 months, and were within the first 12 weeks of a new primary tumour or had a diagnosis of progression. Patients were randomly assigned (1:1), by block design using a computer-generated sequence, either to early and systematic integration of palliative care into oncological care, or standard oncological care alone in a setting where all patients are offered multidisciplinary oncology care by medical specialists, psychologists, social workers, dieticians, and specialist nurses. The primary endpoint was change in global health status/quality of life scale assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (EORTC QLQ C30) at 12 weeks. The McGill Quality of Life Questionnaire (MQOL), which includes the additional existential wellbeing dimension, was also used. Analysis was by intention to treat. This trial is ongoing, but closed for accrual, and is registered with ClinicalTrials.gov, number NCT01865396.

Findings: From April 29, 2013, to Feb 29, 2016, we screened 468 patients for eligibility, of whom 186 were enrolled and randomly assigned to the early and systematic palliative care group (92 patients) or the standard oncological care group (94). Compliance at 12 weeks was 71% (65 patients) in the intervention group versus 72% (68) in the control group. The overall quality of life score at 12 weeks, by the EORTC QLQ C30, was 54·39 (95% CI 49·23–59·56) in the standard oncological care group versus 61·98 (57·02–66·95) in the early and systematic palliative care group (difference 7·60 [95% CI 0·59–14·60]; p=0·03); and by the MQOL Single Item Scale, 5·94 (95% CI 5·50–6·39) in the standard oncological care group versus 7·05 (6·59–7·50) in the early and systematic palliative care group (difference 1·11 [95% CI 0·49–1·73]; p=0.0006).

Interpretation: The findings of this study show that a model of early and systematic integration of palliative care in oncological care increases the quality of life of patients with advanced cancer. Our findings also show that early and systematic integration of palliative care is more beneficial for patients with advanced cancer than palliative care consultations offered on demand, even when psychosocial support has already been offered. Through integration of care, oncologists and specialised palliative care teams should work together to enhance the quality of life of patients with advanced cancer.

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Research in context

Evidence before this study

We searched PubMed for evidence regarding the effectiveness of early palliative care on patient related outcomes in the cancer setting in October 2011. The search was last updated in December 2013. We used the search terms "early palliative care", "integrated care", "integrated palliative care", "integration of palliative care in regular treatment", "advanced cancer", "oncology", "quality of life", and "care pathways". The reference lists of all identified studies were screened for additional relevant studies. Primary research and phase 2 and phase 3 randomised controlled trials on the effect of early palliative care on patient-related outcomes in oncology were included. We restricted our search to articles published between Jan 1, 2005, and Nov 31, 2013. This study is based on strong evidence from phase 2 and phase 3 randomised controlled trials, in which patients with advanced cancer were offered palliative care in combination with standard oncological treatment early in the disease course, which showed that early integration of palliative care in oncology led to significantly improved quality of life and other beneficial patient outcomes.

Added value of this study

Our findings are consistent with other studies showing that early and systematic integration of palliative care in oncological care improves quality of life of patients with cancer. Our findings show the positive effect of our complex intervention that is based on several core components: training of the palliative care team, the provision of semi-structured consultations by palliative care nurses, frequent symptom assessment and participation in multidisciplinary oncology meetings, and reporting in the electronic patient file.

Implications of all the available evidence

The skills and attitudes needed for early and systematic integration of palliative care into oncology trajectories suggests a need for education and training of the palliative care professionals. Further research is needed to establish which components of early palliative care are more effective than others, which components should be further improved, and whether this intervention has a positive effect on the family caregivers of patients with advanced cancer.

Introduction

WHO underlines the importance of providing palliative care early in the disease trajectory of patients suffering from a life-limiting illness.[1] Similarly, the American Society of Clinical Oncology recommends that palliative care services should start early in the disease course concurrent with active treatment of patients with advanced cancer.[2] Traditionally, oncologists have been responsible for guiding patients in treatment decisions, often with a focus on the use of chemotherapy or radiotherapy to control disease progression.[3] The physical, psychological, and social needs of patients with cancer are less often assessed and addressed.[4] Over the past few years, a growing number of studies have focused on the effects of early integration of palliative care for patients with cancer.

A systematic review[5] identified six trials in North America and one in Europe evaluating the effect of early integration of palliative care into oncology care.[6–12] These interventions varied from monthly face-to-face consultations with palliative care physicians[6,7] to telephone-based consultations with an advanced practice nurse.[8,9] Study populations differed; five trials included patients with different cancer types[7–11] and two focused on specific cancer types: advanced non-small-cell lung cancer[6] and advanced pancreatic cancer.[7,12] In all but one trial,[9] the overall patient-reported quality of life at 12 weeks was the primary outcome.[12] Two trials[6,12] reported a positive effect on overall quality of life 12 weeks after different early integration of palliative care interventions into standard oncological care were investigated, whereas three studies found a positive effect on quality of life after the first 12 weeks.[7,9,10]

The observed benefit of early palliative care integration in oncology has been suggested to be due to the increased psychosocial support that patients receiving early palliative care have compared with those undergoing standard oncological care.[3] In Belgium, psychosocial care delivered by specialist nurses, social workers, dieticians, and psychologists specifically trained in oncological care is part of the routine oncology care and free of charge,[13] with 350 full-time equivalent (FTE) nurses, 350 FTE psychologists, and 175 FTE social workers available per 100 000 cancer cases (2009 data).[14] Hospital-based palliative care is also available without financial barriers, but resources are less extensive: hospital-based palliative care teams are formed by 0·5 FTE specialised nurses, 0·5 FTE palliative care physicians, and 0·5 FTE palliative care psychologists per500 hospital beds.[15] The proportion of patients with cancer referred to palliative care in Belgium is approximately 56%, with a median time to first referral before death of 16 days (IQR 7–31).[16] In this setting, where standard oncological care is multidisciplinary and psychosocial support is offered to all cancer patients, it is not known whether early and systematic integration of palliative care could have added value. Therefore, we did a randomised controlled trial to compare the effect of early and systematic integration of palliative care into oncological care versus standard oncological care alone on quality of life in this setting in Belgium.

Methods

Study design and participants

In this non-blinded, randomised, controlled trial, we recruited patients with advanced cancer from the Medical Oncology, Thoracic Oncology, and Digestive Oncology departments of Ghent University Hospital in Flanders, Belgium. Patients were identified for recruitment by a trained clinical research assistant (who attend weekly staff meetings) and the treating oncologists. Both outpatients and inpatients were considered for inclusion. Eligible patients were 18 years or older, and had an advanced cancer diagnosis (histologically or cytologically confirmed) due to a solid tumour, a European Cooperative Oncology Group performance status of 0–2, an estimated life expectancy of 12 months (assessed by the treating oncologist), were within the first 12 weeks of a new primary tumour or had a diagnosis of progression, and were able to read and respond to questions in Dutch. Patients recruited from a hospital other than Ghent University Hospital had to be within the first 12 weeks of a disease progression event or still on first-line treatment. Once enrolled in the trial, these patients received further treatment and care at Ghent University Hospital to ensure consistent management.

Patients with haematological malignancies were excluded because they have a less predictable disease trajectory than those presenting with solid tumours. Patients were excluded if they had had one or more palliative care consultation at any time, or one palliative care consultation in the 6 months before diagnosis or disease progression. Patients deemed cognitively impaired at the discretion of the oncologist and psychologist during the staff meetings were not eligible.

The Ethical Committee of the Ghent University Hospital approved the study protocol; oncologists described the study to patients and all participants provided written informed consent. The full protocol of the study has been previously published.[17]

Randomisation and masking

Patients were randomly assigned (1:1) to either systematic early integration of palliative care in oncological care or to usual oncological care. We generated the randomization list using the permuted block method (block size of 4), stratified according to treating department. Computer-generated sequences were created by a statistician using the PLAN procedure in SAS (version 9.4). The allocation sequence was only available to an independent administrative assistant and was unknown to the investigators. The research assistant enrolled the patients and obtained patient study numbers and the corresponding allocation from the administrative

assistant. Masking those individuals giving the intervention, those assessing the outcomes and analysing the data was not possible.

Procedures

Standard oncology care in all the participating departments at Ghent University Hospital (Flanders, Belgium) is provided by a multidisciplinary team, including oncologists, other medical specialists, psychologists, social workers, dieticians, and specialist nurses. All patients with advanced cancer have one introductory consultation with a specialist nurse trained in oncological care with a broad knowledge of specific tumour types and its associated complications and side-effects of commonly used therapies (eg, radiotherapy), a dietician, and a psychologist at the start of their treatment; follow-up consultations are at the discretion of the patient.[17] In routine clinical practice, the palliative care team is only involved on demand, often late in the disease trajectory, and their services are not systematically offered to all patients from oncology departments.

Palliative care consultations are available to all patients for whom a curative treatment is no longer available, and are led by nurses who can refer patients to the palliative care physician for refractory symptoms, exploration of complex question related to the end-of-life (sedation, euthanasia), and clarification of medical situations related to palliative or end-of-life care. The palliative care physician involved in this study has a specialty degree in anaesthesiology and is a trained professional in specialised palliative care. Over the past 5 years, the palliative care team had, on average, 820 consultations per year in a hospital that consisted of 1061 hospital beds.

In this study, on the basis of standard care practices, patients were assumed to have received the introductory consultation after the initiation of treatment; however, consultations before baseline could not be assessed. All patients could have further consultations with the specialist nurse, dietician, and psychologist on demand. Some patients in the standard oncology care group had a consultation with the palliative care team at the patient's or physician's discretion, but were not excluded from the study or moved to the intervention group.

Patients assigned to the early integration of palliative care in oncological care group had a first consultation with a specialised palliative care nurse within 3 weeks of enrolment. Consultations for patients assigned to the control group were organised on demand. Hospital consultations between patients and palliative care nurses were organised monthly until the patient's death, and coincided with planned oncological staff meetings. The palliative care physician visited patients after referral from the palliative care nurse; these nurse recommendations were not predefined by protocol. Our early palliative care intervention in the Belgian health-care system used a previously published study[6] of early palliative care for patients with non-small-cell

lung cancer based in the USA as a guide. The main difference between the studies is that the previous palliative care intervention was led by physicians, whereas the present is led by palliative care nurses.

The intervention consisted of four major components:

(1) Training sessions by oncologists to inform palliative care nurses and the physician about cancer treatments typically administered early in the disease trajectory, and their associated side-effects. These training sessions were provided before the initiation of the trial and deemed necessary because the palliative care team had little experience of providing early palliative care. One training session included the use of the intervention documents and the administration of the Edmonton Symptom Assessment Scale (ESAS).[18]

(2) Semi-structured, monthly palliative care consultations by palliative care nurses allowed for individualised patient care. These consultations were based on an interview form (appendix p 2), focusing on illness understanding and perception, symptom burden, psychological coping, spiritual coping, and medical decision making**.** If needed, patients were referred to other health-care professionals through completion of a referral checklist by palliative care nurses at the end of every consultation.

(3) Monthly symptom assessments using ESAS[18] by palliative care nurses. Nurses were instructed to discuss important changes in the ESAS symptom scores, and high scores (a cut-off score was not prespecified by protocol) with the patient and the treating physician.

(4) Integration of palliative care into oncological care through the participation of the palliative care nurses in the weekly multidisciplinary oncology meetings and their reporting in the electronic patient file.

After giving informed consent and before randomisation, all screened patients completed a demographic questionnaire measuring baseline characteristics. We also collected information about treatments being received at baseline from the medical records of the patients. Enrolled patients completed follow-up questionnaires administered by the data manager at 12, 18, and 24 weeks, and 6-weekly thereafter until death. Patients who were not willing or able to complete the questionnaires at the hospital received them by mail.

Outcomes

The primary outcome was change in overall quality of life from baseline at 12 weeks, measured by the global health status/quality of life scale of the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 items (EORTC QLQ C30; version 3).[19] Overall changes in quality of life from baseline were also measured at 18 and 24 weeks. We used the Single Item Scale and overall summary score of the McGill Quality of Life Questionnaire (MQOL)[20] as an exploratory measure of overall quality of life. The

Single Item Scale was used because it is the closest to the global health status/quality of life scale of the EORTC QLQ C30.

Protocol-specified[17] secondary endpoints reported here include changes in patient's mood; understanding of illness; frequency of contact with a psychologist, dietician, social worker, or a specialist nurse between baseline and 24 weeks; EORTC QLQ C30 functioning and symptoms scales and MQOL functioning scales; and overall survival. Additional protocol-specified secondary endpoints not reported here include patient illness trajectory and end-of-life care; caregiver's mood, understanding of the patient's illness, satisfaction with care, and impact on quality of life; and impact on advance-care planning and end-of-life decision making, as reported by the patient's physician.

We measured changes in patient's mood with the Hospital Anxiety and Depression Scale (HADS),[21] a 14-item self-assessment scale that consists of two subscales that assess anxiety and depression symptoms, and the Patient Health Questionnaire 9 (PHQ-9), a nine-item self-assessment questionnaire that detects symptoms of a major depressive disorder based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders IV.[22,23]

Illness understanding was defined as disease and prognostic understanding by cancer patients and measured with forward-backward translation of the questionnaire used by Temel and colleagues,[6] containing questions about prognosis (curable *vs* non-curable), the goals of therapy (to help the patient to live longer, to try to make them feel better, or to get rid of or cure their cancer), and health perception (relatively healthy; seriously, but not terminally ill; or seriously and terminally ill). Median overall survival was defined as the time from patient enrolment to death.

We obtained data on the informal caregivers' mood, quality of life, illness understanding, and satisfaction with care with the HADS,[21] the Short Form-36 Health Survey (SF-36, which measures eight domains of health-related quality of life: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional health, and mental health, as well as physical and mental component scores),[24] Temel and colleagues'[6] questionnaire for illness understanding, and the FAMCARE tool (a 20-item measure for family satisfaction with care measuring, including four subscales: information giving, physical patient care, psychosocial care, and availability of care).[25]

Oncologists and general practitioners were asked to complete a validated Dutch questionnaire that has been used several times in nationwide end-of-life decision incidence studies in Flanders, Belgium,[26,27] to collect information about advance-care planning and end-of-life decision making.

Statistical analysis

We analysed data obtained up to April 3, 2017. With 59 patients in each group, the study had a power of 80% to detect a 12-point difference in the global health status/quality of life scale EORTC QLQ C30 score from baseline to 12 weeks between both study groups assuming a SD of 23·0. Based on a previous study,[6] we expected an overall drop-out rate of 35% (20% related to death before 12 weeks, 15% drop out for other reasons), accounting for the planned inclusion of 182 patients. In April, 2013, we set out to include patients with cancer of the upper-gastrointestinal tract. In March, 2014, the protocol was amended to include additional patients with a solid tumour with a life expectancy of about 1 year to compensate for the slow enrolment of patients. We analysed data by intention to treat, meaning that all patients who were randomly assigned (including those who died after enrolment) were included in the analysis.

Patients' responses to questions about health-related quality of life assessed by EORTC QLQ C30 and MQOL were scored into scales. The EORTC QLQ C30 incorporates five functional scales (ie, physical, role, cognitive, emotional, and social), three symptom scales (ie, fatigue, pain, and nausea and vomiting), a global health status/quality of life scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (ie, dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial effect of the disease. All scales and items are converted to a 0–100 scale.[19] The MQOL incorporates a Single Item Scale of global quality of life and four subscales, measuring four relevant domains of quality of life (ie, physical, psychological, existential/spiritual, and social). A summary score weights these domains equally.[20]

Patients' mood evaluation included depression evaluated by the HADS items 2, 4, 6, 8, 10, 12, and 14, and anxiety assessed by items 1, 3, 5, 7, 9, 11, and 13. Items in the HADS were averaged into a score range from 0 to 21 (maximum distress). Depression was also assessed by the PHQ-9 items 1–9, with a cut-off threshold score of 8 or more, with higher scores indicating worse depression.[22,23] The results of the validated Dutch questionnaire are yet to be analysed.

The effect of intervention on the primary outcome and other outcomes was assessed by multivariate regression analyses adjusted for baseline scores. We applied multiple imputation (n=50) for missing data, using the fully conditional specification method of the multiple imputation procedure in SAS. The predictors of the imputation model were age, sex, department, ECOG performance status, group, treatment, tumour site, and days between diagnosis and baseline. We applied a linear regression model with score at baseline, group, and department as predictor variables on the imputed dataset using the MIANALYZE procedure. A sensitivity

analysis was done to analyse the effect of missing data handling by using complete case analysis. We used the Mann-Whitney *U* test to examine differences in consultations between study groups. For the secondary outcomes of mood and illness understanding, we did logistic regression analysis on the complete cases adjusting for the stratification factor. We did a Spearman correlation between performance status and compliance with the intervention, which is measured by the number of consultations with the palliative care team. A Kaplan-Meier plot and a log-rank test were used to examine the effect of early and systematic integration of palliative care on overall survival. We did statistical analysis using SPSS software (version 24) and SAS software (version 9.4). This trial is registered with ClinicalTrials.gov, number NCT01865396.

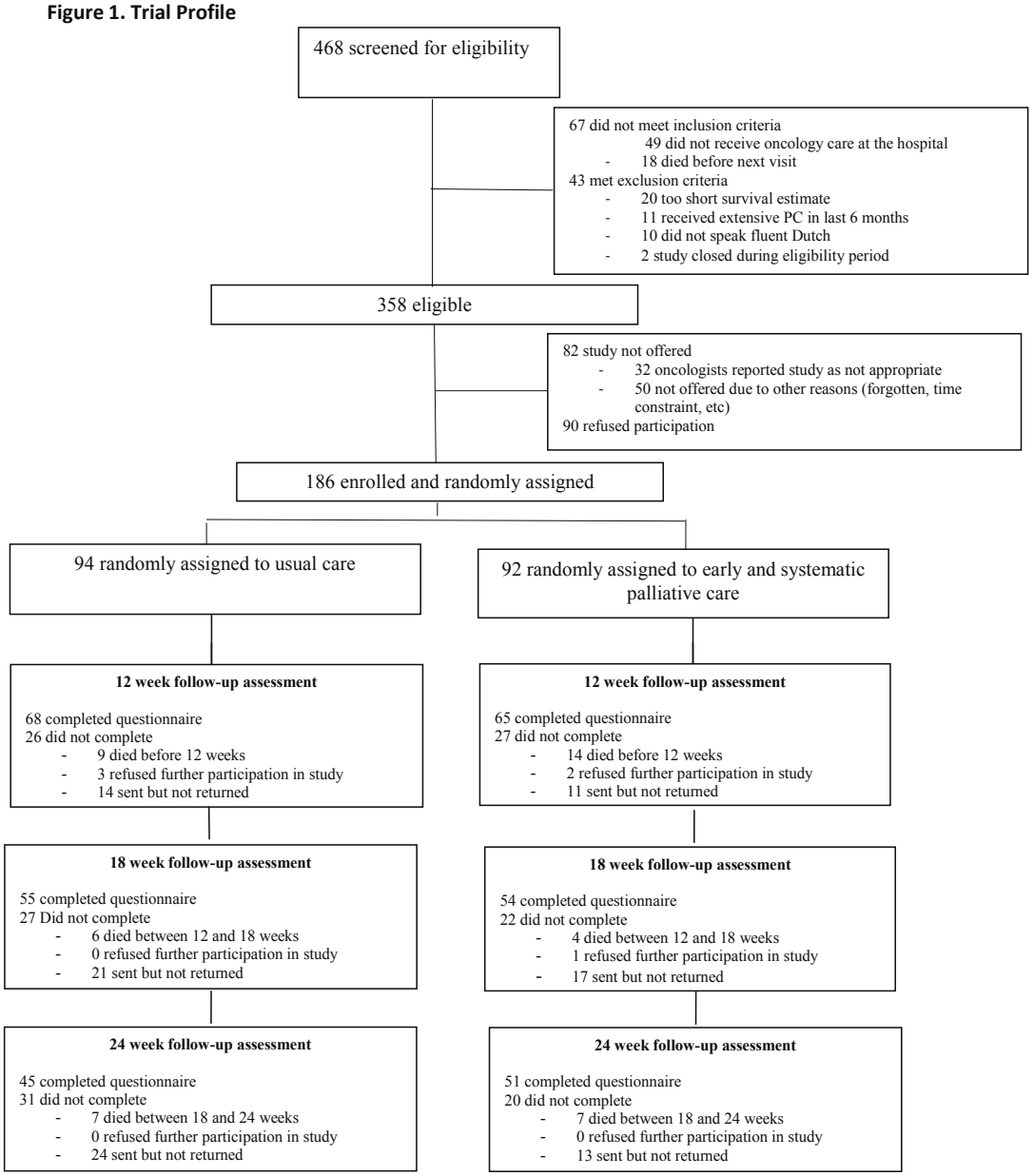
Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Results

From April 29, 2013, to Feb 29, 2016, we screened 468 patients with incurable, advanced cancer, of whom 186 were enrolled and randomly assigned to receive either early and systematic palliative care in oncology care (92 patients) or to standard oncology care (94 patients; figure 1). The demographic baseline characteristics of the participants are shown in table 1.

Figure 1. Trial Profile



Compliance at 12 weeks was 71% (65 patients) in the intervention group versus 72% (68) in the control group. Compliance for questionnaires sent by post was 87 (75%) of 118 questionnaires at 12 weeks, 84 (71%) of 116 at 18 weeks, and 78 (72%) of 109 at 24 weeks; and 46 (96%) of 48 questionnaires at 12 weeks, 25 (83%) of 30 at 18 weeks, and 18 (90%) of 20 at 24 weeks for questionnaires administered at the hospital. The numbers of deaths at 12, 18, and 24 weeks by cancer type are shown in table 2.

Table 2. Number of deaths reported at 12, 18 and 24 weeks by cancer type.

	12 weeks		18 weeks		24 weeks	
	Usual care (n=94)	Early and systematic palliative care (n=92)	Usual care (n=94)	Early and systematic palliative care (n=92)	Usual care (n=94)	Early and systematic palliative care (n=92)
Total	9 (10%)	14 (15%)	15 (16%)	18 (20%)	22 (23%)	25 (27%)
Gastrointestinal cancer	4 (4%)	5 (5%)	6 (6%)	6 (7%)	10 (11%)	11 (12%)
Lung cancer	3 (3%)	5 (5%)	4 (4%)	6 (7%)	5 (5%)	6 (7%)
Head and neck cancer	0 (0)	0 (0)	1 (1%)	0 (0%)	1 (1%)	0 (0%)
Breast cancer	1 (1%)	1 (1%)	2 (2%)	3 (3%)	4 (4%)	3 (3%)
Melanoma	1 (1%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)	2 (2%)
Genitourinary cancer	0 (0)	2 (2%)	1 (1%)	2 (2%)	1 (1%)	3 (3%)

Of the 92 patients in the early and systematic palliative care group, 82 (89%) had at least one consultation with a nurse from the palliative care team from baseline to 18 weeks (median 3·0 consultations [IQR 1·0–4·0]; figure 2) and 10 (11%) did not have any consultations: two (2%) had died, two (2%) did not visit the hospital by 18 weeks, one (1%) had stopped participation by 12 weeks, and five (5%) did not have a consultation despite being eligible. 25 (27%) patients had at least one visit with the palliative care physician. By 24 weeks, 55 (60%) patients had at least three consultations with the palliative care nurses (3·0 [IQR 2·0–5·0]) and 32 (35%) patients had at least one consultation with the palliative care physician.

In the standard oncology care group, 17 (18%) of 94 patients had at least one consultation with a palliative care nurse and one (1%) had one consultation with the palliative care physician from baseline to 18 weeks (figure 2). By 24 weeks, 12 (13%) patients had at least three consultations with the palliative care nurses and one (1%) had one consultation with the palliative care physician. No correlation was found between functional status and number of consultations with the palliative care team (Spearman's ρ=0·1; 95% CI −0·10 to 0·30]; p=0·32).

Table 1: Baseline Characteristics

Variable	Usual Care (n=94)	Early and systematic palliative care (n=92)
Age, years	65.0 (57.0-71.0)	64.5 (57.3-71.0)
Sex		
Women	25 (27%)	33 (36%)
Men	69 (73%)	59 (64%)
Living Situation*		
Home (Alone)	16 (17%)	14 (15%)
Home (Cohabiting)	77 (82%)	73 (80%)
Living with family (not at home)	1 (1%)	3 (3%)
Care facility	0 (0)	1 (1)
Highest level of education |		
Lower than high school	2 (2%)	3 (3%)
Lower level in high School	26 (27%)	18 (20%)
Higher level in high school	37 (39%)	35 (39%)
College, university, or other	30 (32%)	33 (37%)
ECOG performance status ∫		
0	22 (23%)	36 (39%)
1	53 (56%	46 (50%)
2	13 (14%)	8 (9%)
3	6 (6%)	2(2%)
Medical department - no (%)		
Digestive Oncology	36 (38%)	35 (38%)
Medical Oncology	32 (34%)	32 (35%)
Thoracic Oncology	26 (27%)	25 (27%)
Tumor Site - no (%)		
Gastrointestinal	36 (38%)	35 (38)
Pancreas	11 (31%)	14 (40%)
Biliary tract	7 (19%)	4 (11%)
Oesophagus	2 (6%)	4 (11%
Gastro-oesophageal	3 (8%)	4 (11%)
Gastric	5 (14%)	2 (6%)
Colorectal	8 (22%	7 (20%)
Lung	26 (28%)	25 (27%)
Head & Neck	12 (13%)	7 (8%)
Breast	7 (7%)	7 (8%)
Melanoma	7 (7%)	8 (9%)
Genitourinary	6 (6%)	10 (11%)
Prostate	3 (50%)	3 (30%)
Blatter	2 (33%)	2 (20%)
Kidney	1 (17%)	5 (50%)
Anticancer therapy at baseline		
Yes	90 (96)	87(95)
No	4(4)	5(5)
Quality of Life at baseline ‖		
EORTC-QLQ C30 Global Health Status/QoL-scale	60.9 ± (18.6)	58.4± (20.1)
McGill quality of life Single Item Scale	7.1±(1.82)	6.8 ±(2.01)

Data are median (IQR), n (%), or mean (SD). Percentages might not total 100% because of rounding. ECOG=Eastern Cooperative Oncology Group. EORTC QLQ C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire version 30. MQOL=McGill Quality of Life Questionnaire. *One value missing from the early and systematic palliative care group. | Three values missing from the early and systematic palliative care group. ∫At screening, all patients with ECOG performance status ≤2 were selected, eight patients deteriorated to ECOG performance status of 3 at baseline; these patients were not excluded from analysis

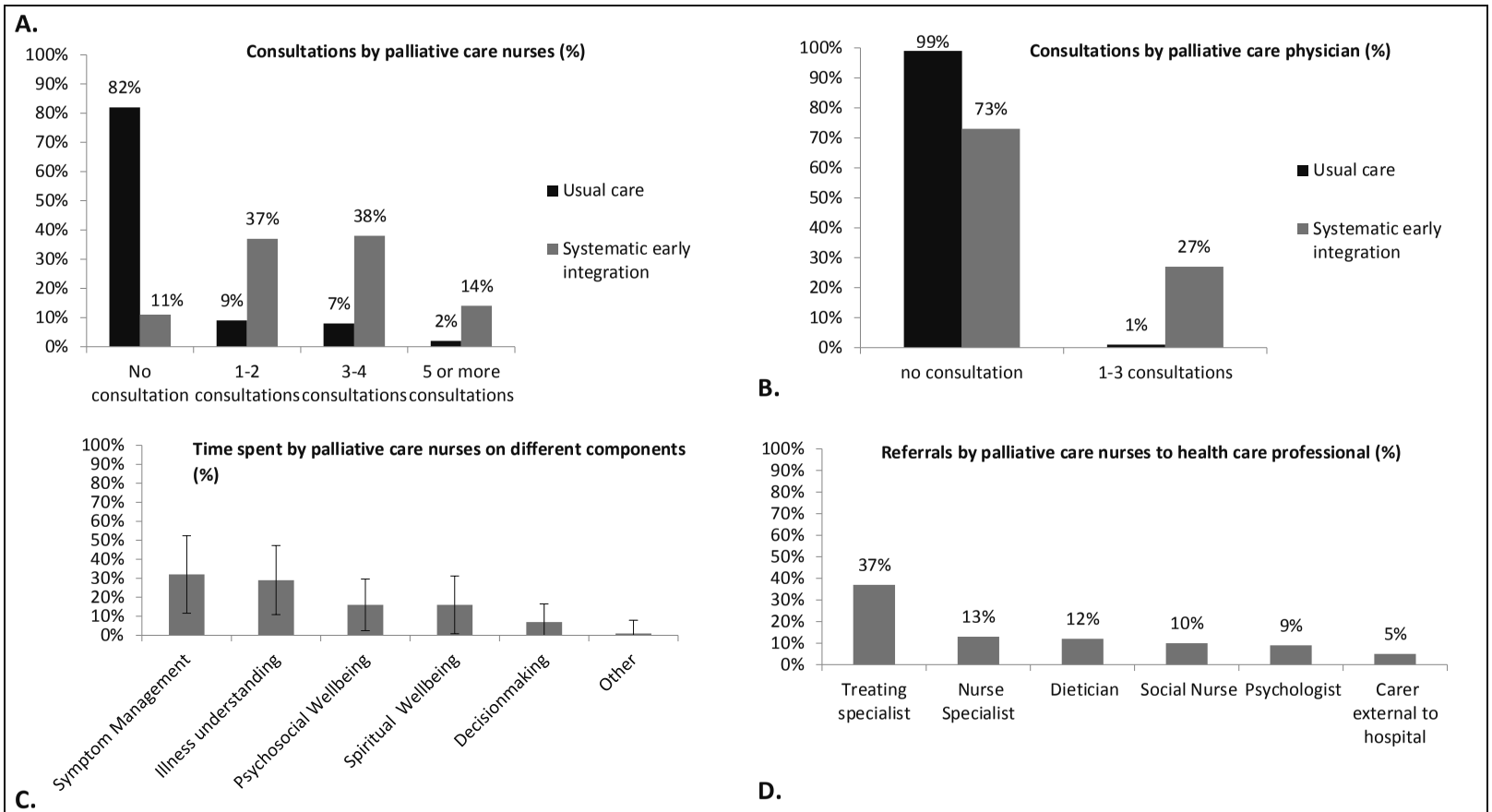


Figure 2. Number and focus of consultations by the palliative care team between baseline and 18 weeks

(A, B) Data are proportions of consultations based on total number of visits during baseline and 18 weeks for both usual care and the intervention group. (C) Bars represent the average percentage of time spent on the different topics over all consultations by palliative care nurses between baseline and 18 weeks in the intervention group. Error bars are SD. (D) Data are proportion of referrals based on total number of visits during baseline and 18 weeks in the intervention group

Overall quality of life 12 weeks after baseline was significantly improved in patients receiving early and systematic palliative care compared to those receiving standard oncology care: the mean global health status/quality of life score by the EORTC QLQ C30 was 61·98 (95% CI 57·02–66·95) in the intervention group versus 54·39 (49·23–59·56) in the standard oncology care group (difference did not meet minimal clinical difference of 10 points; difference 7·60 [0·59–14·60], p=0·03, Cohen's *d*=0·4), and by the MQOL Single Item Scale was 7·05 (6·59–7·50) in the early and systematic palliative care group versus 5·94 (95% CI 5·50–6·39) in the standard oncological care group (difference 1·11 [95% CI 0·49–1·73]; p=0·0006). The positive effect of early and systematic palliative care on overall quality of life assessed by both scales remained significant at 18 weeks (table 3)

At the time of the data cutoff, 121 (65%) of 186 participants had died and the median follow-up was 284 days (IQR 144–489). There was no significant difference in the median overall survival: 312 days (95% CI 190–434) in the early and systematic palliative care group versus 343 days (253–433) in the standard oncology care group (p=0·97; figure 3).

The symptom scales and items of the EORTC QLQ C30 did not significantly differ between groups, except for fatigue and diarrhoea at 18 weeks (appendix p 3). The results of overall quality of life, functioning, and symptoms at 24 weeks are presented, but due to a substantial decrease in power because of total deaths (47 [25%] of 186 patients) and missing data (37 [20%] non-responders of 186 patients) at this timepoint, no clear conclusions can be drawn (table 3; appendix table 1).

Sensitivity analyses with complete cases (ie, excluding cases for which values are missing) showed similar results for the EORTC QLQ C30 and MQOL at all time points, except for the role functioning scale, assessed by the EORTC QLQ C30, which differed at 12 weeks between the groups (appendix Table 2).

Patients' mood, including depressive symptoms, as measured by the HADS and the PHQ-9, and anxiety assessed by the HADS anxiety subscale did not differ significantly between study groups at any of the study time points (12, 18, and 24 weeks; appendix table 3).

The perception of the goals of therapy differed significantly between study groups at 12 weeks, but not at 18 and 24 weeks (appendix table 4). The groups did not differ in understanding of prognosis at any of the study timepoints. Similarly, there was no significant difference in the odds of reporting to be relatively healthy versus seriously and terminally ill at any of the study time points.

Consultations before baseline could not be assessed—eg, patients who were already receiving treatment at the hospital and have had introductory consultations and possible follow-up consultations with the paramedical specialists. There were no significant differences between study groups in the number of consultations with a social care nurse (p=0·87), dietician (p=0·32), or specialist nurse (p=0·28) between 18 weeks and baseline; or between 24 weeks and baseline with social care nurse (p=0·07), dietician (p=0·95), or specialist nurse (p=0·99). However, the number of consultations with a psychologist between baseline and 18 weeks significantly differed between groups: 34 (37%) of 92 patients from the intervention group had at least one consultation with a psychologist compared with 21 (22%) of 94 patients in control group (p=0·02; appendix figure 2). No significant difference was found between baseline and 24 weeks.

Data regarding whether physicians discussed advance care planning and end-of-life care with their patients, patient quality of life near death, and caregiver-reported outcomes will be reported elsewhere.

Table 3: **Mean scores and differences (baseline adjusted) in quality-of-life and functioning scales of the EORTC QLQ C30 and the MQOL questionnaire at 12, 18, and 24 weeks**

	12 weeks					18 weeks					24 weeks				
	Mean score [95% CI]		Difference (95% CI)	P value	Effect size‖ (Cohen 's d')	Mean score [95% CI]		Difference (95% CI)	P value	Effect size‖ (Cohen's d')	Mean score [95% CI]		Difference (95% CI)	p-value	Effect size‖ (Cohen's d')
	Usual Care (n=94)	Early and systematic palliative care (n=92)				Usual Care (n=94)	Early and systematic palliative care (n=92)				Usual Care (n=94)	Early and systematic palliative care (n=92)			
Quality-of-life summary scores															
EORCT QLQ-C30 quality of –life score	54.39 (49.23-59.56)	61.98 (57.02-66-95)	7.60 (0.59-14.60)	**0.03**	**0.4**	54.70 (49.09-60.32)	64.18 (58.78-69.59)	9.48 (2.13-16.82)	**0.01**	**0.5**	56.2 (47.5-65.0)	64.6 (58.1- 71.1)	8.4 (-2.3 - 19.0)	0.12	0.4
MQOl Single Item Scale	5.94 (5.50-6.39)	7.05 (6.59-7.50)	1.11 (0.49-1.73)	**0.0006**	**0.6**	5.51 (4.96-6.07)	7.00 (6.45-7.55)	1.48 (0.75-2.22)	**0.0001**	**0.8**	5.95 (5.16-6.74))	6.92 (6.25-7.60)	0.98 (-0.03-1.98)	0.06	0.5
MQOL Summary Score	6.76 (6.38-7.14)	7.16 (6.80-7.52)	0.40 (-0.11-0.90)	0.12	0.3	6.60 (6.17-7.02)	6.99 (6.61-7.38)	0.39 (-0.12-0.91)	0.13	0.1	6.48 (5.91-7.06)	7.19 (6.72-7.65)	0.70 (0.01- 1.39)	**0.047**	**0.5**
EORTC QLQ C30 Functioning scores															
Physical functioning	62.75 (57.20-68.29)	68.81 (63.45-74.18)	6.07 (-1.30-13.43)	0.11	0.2	55.49 (48.90-62.08)	66.76 (60.44-73.07)	11.26 (2.58-19.95)	**0.01**	**0.5**	55.73 (48.04-63.42)	67.56 (60.91-74.22))	11.83 (2.15-21.51))	**0.02**	**0.5**
Emotional functioning	71.25 (65.95-76.56)	73.22 (67.92-78.52)	1.97 (-2.61-6.79)	0.59	0.1	64.69 (57.57-71.82)	73.54 (66.72-80.37)	8.85 (-0.54-18.23)	0.06	0.4	67.8 (58.21-77.35))	72.62 (65.38-79.87)	4.84 (-6.89-16.58)	0.41	0.2
Social functioning	70.67 (64.72-76.62)	73.52 (67.24-79.80)	2.85 (-5.08-10.78)	0.49	0.1	66.92 (58.14-75.69)	69.65 (60.93-78.37)	2.73 (-8.95-14.42)	0.64	0.1	63.42 (53.43-73.42)	76.30 (68.56 - 84.09)	12.88 (0.21 - 25.55)	**0.047**	**0.5**

Role functioning assessed	53.55 (46.82-60.29)	63.21 (56.47-69.95)	9.7 (0.13-19.18)	0.05	0.3	45.44 (36.53-54.35)	61.4 (52.59-70.21)	15.96 (3.96-27.96)	**0.01**	**0.5**	53.61 (41.91-65.31)	58.07 (48.61-67.53)	4.46 (-9.83-18.75)	0.53	0.1
Cognitive functioning	78.28 (73.67-82.88)	85.51 (80.95-90.06)	7.23 (0.97-13.49)	**0.02**	**0.3**	73.52 (66.14-8.91)	76.87 (67.79-83.96)	3.34 (-6.44-13.13)	0.50	0.1	74.29 (65.53-83.04))	81.02 (74.15-87.90)	6.74 (-4.08-17.55)	0.22	0.3
MQOL Functioning scores															
Physical functioning	6.69 (6.11-7.26)	6.94 (6.37-7.51)	0.25 (-0.52-1.03)	0.52	0.1	6.58 (5.71-7.45)	6.25 (5.44-7.06)	-0.33 (-1.48-0.82)-	0.57	-0.1	5.82 (4.63-7.01)	6.72 (5.81- 7.64)	0.90 (-0.51-2.31)	0.21	0.3
Psychological functioning	6.75 (6.19-7.30)	7.12 (6.55-7.70)	0.37 (-0.45-1.19)	0.37	0.2	6.50 (5.87-7.14)	7.14 (6.55-7.74)	0.64 (-0.16-1.43)	0.11	0.3	6.71 (5.90-7.51)	7.50 (6.96- 8.04)	0.80 (-0.11-1.71)	0.09	0.3
Support functioning	7.65 (7.24-8.06)	7.92 (7.52- 8.32)	0.27 (-0.27-0.81)	0.33	0.1	7.58 (7.08-8.07)	7.69 (7.26- 8.13)	0.27 (-0.52- 0.74)	0.72	0.1	7.18 (6.61-7.74)	7.67 (7.18- 8.16)	0.50 (-0.26-1.25)	0.19	0.3
Existential functioning	6.43 (6.02-6.84)	7.17 (6.76-7.58)	0.74 (0.19-1.28)	**0.008**	**0.5**	6.33 (5.83-6.84)	6.93 (6.46-7.40)	0.59 (-0.02-1.20)	0.06	0.4	6.29 (5.63-6.93)	7.24 (6.72- 7.76)	0.96 (0.17- 1.74)	**0.02**	**0.6**

Higher mean scores represent a better quality of life or functioning. Imputations (n=50) with predictors: age, sex, department, ECOG performance status, group, treatment, tumour site, and days between diagnosis and baseline. p<0·05 indicates significance. EORTC QLQ C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire version 30. MQOL=McGill Quality of Life Questionnaire. ECOG=Eastern Cooperative Oncology Group. *Cohen's *d*: the difference between the group means divided by the pooled SD; small 0·2, medium 0·5, large 0·8.[28]

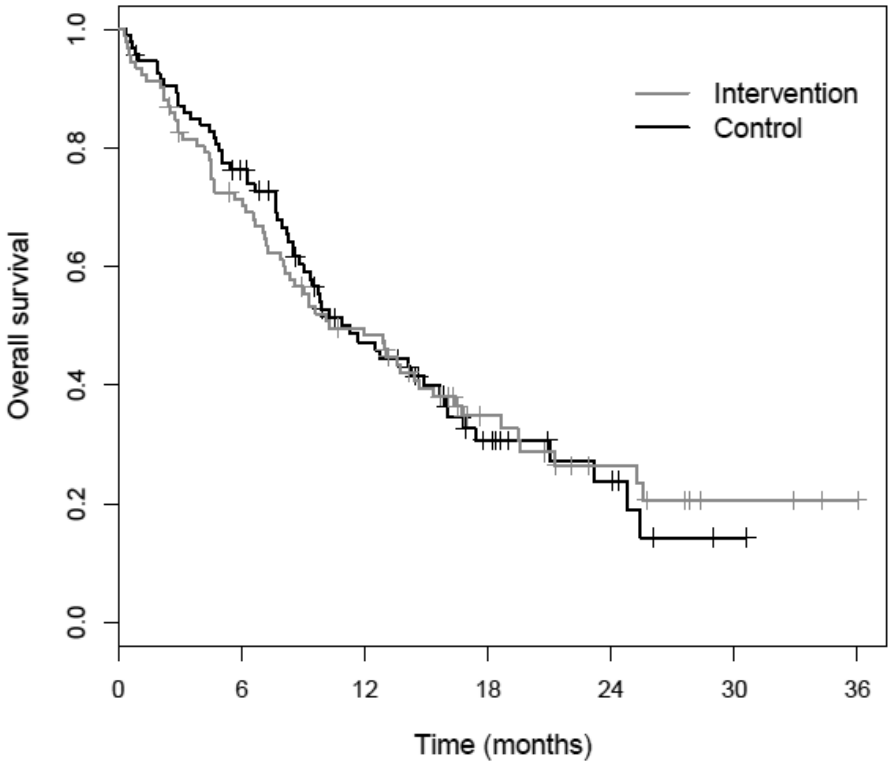


Figure 3. Overall survival

Discussion

In this trial, early and systematic integration of palliative care into usual oncology care significantly improved overall quality of life compared with usual care, measured by the global health status/quality of life scale of the EORTC QLQ C30 and the single item scale of the MQOL at 12 weeks, but did not reach minimal clinical significance (difference of 10 points).[19] The results remained significant at 18 weeks. The intervention also resulted in a significant increase in the number of consultations with clinical psychologists from the oncology team by 18 weeks compared with standard oncology care. An exploratory analysis showed benefits in cognitive, role, and physical functioning, fatigue, and existential wellbeing in patients who received early and systematic palliative care compared with those who receive usual care. No differences in survival were found between the groups.

To our knowledge, this is the first time that early and systematic integration of palliative care in oncological care has improved the overall quality of life of patients with advanced cancer, of whom most were offered psychosocial support by professionalised caregivers. Conclusions regarding the mechanisms of early palliative care cannot be made with the current study design. However, we believe that improved overall quality of life might be related to the differences in the focus of oncology and palliative care. Oncology professionals and psychosocial interventions mostly focus on symptom burden caused by the disease and treatment, whereas palliative care professionals mainly focus on a patient's quality of life—eg, spending time with family and friends, or partaking in day-to-day activities.

Two previous trials of early palliative care integration in oncology care showed a significant improvement in quality of life at 12 weeks[6,12] and three identified an improvement at later timepoints.[7,9,10] The intervention proposed in this trial found significant improvements in quality of life at both 12 and 18 weeks. Additionally, studies[6,10] with a similar intervention model based on structured, monthly palliative care consultations had smaller effect sizes for overall quality of life, measured by the Functional Assessment of Cancer Therapy-General scale (Cohen's *d* 0·3–0·5), than our study, measured by the EORTC QLQ C30 and MQOL (0·4–0·8). This study adds value to the literature by showing that a nurse-led intervention of early and systematic integration of palliative care[8] in a country that does not allow specialized nurses to prescribe treatments, as opposed to physician-led interventions[6], is also beneficial for patients with advanced cancer who are offered standard multidisciplinary psychosocial support in usual oncology care. Our findings underline the importance of providing early and planned semi-structured palliative care consultations that allow patients to discuss all aspects of palliative care at their own pace. This approach contrasts with the usual care group, in which palliative care consultations were only arranged on demand and often late in the disease course. Our results also provide evidence of the importance of the integration of palliative care into oncological care,

which was achieved by the participation of palliative care nurses in multidisciplinary oncology meetings and by their active referral roles.

Unlike previous studies[6,9], we did not observe an improvement in overall survival. The mechanism underlying an overall survival benefit in this setting is still to be defined, but less aggressive treatment regimens have been suggested as a possible explanation[6,9]. Our intervention might have had less of an effect on aggressive treatment choices of patients because the role of the palliative care physician in our trial was small.

The intervention protocol of our study included monthly consultations with a palliative care nurse; however, half of the participants in the intervention group had consultations less often than monthly in contrast with similar intervention models that have succeeded in providing monthly palliative care consultations to most participants; the reduced number of consultations achieved in this study might be due to the relatively small size of the palliative care team.[6,7] Future research in which participants are randomly assigned to different targeted frequencies of early palliative care consultations is necessary to be able to draw conclusions about the number of consultations needed to improve the quality of life of patients with advanced cancer.

Notably, we also observed a significant difference between both groups in the number of consultations with the clinical psychologists, but not with other members of the team. This difference could be influenced by an increased referral of patients in the intervention group to the psychologists by the palliative care nurses because these nurses participated in multidisciplinary staff meetings, at which the nurses could discuss the content of their consultations; it is possible that psychologists, who also attended these meetings, organised consultations with patients on the basis of this information. However, despite the increased number of consultations with psychologists in the group that received early and systematic palliative care, there was no significant difference in psychological outcomes (eg, depression, anxiety, and emotional functioning). The follow-up time (18 weeks) might have been too short or the psychological intervention too limited to observe an effect.

Several other patient-reported outcomes were improved in patients who had early and systematic integration of palliative care. Cognitive functioning and existential wellbeing were significantly improved at 12 weeks, as were physical functioning and role functioning at 18 weeks. This delayed effect on symptom burden is in line with other research that did not find evidence of decreased symptom burden at 3 months, but showed a decrease by 4 months.[10] By contrast with the functioning scales, perceived overall quality of life consistently improved at both 12 and 18 weeks. This finding indicates that overall quality of life is more than an aggregate score of functioning and is a sensitive reflection of how the patient perceives their overall quality of life. Fatigue and diarrhoea were also significantly different between groups, the reasons for which are not clear.

For the primary analysis, we chose to include all randomised participants, as opposed to a modified intention-to-treat analysis that excludes those patients who died at each time point. This analysis strategy avoids bias because all patients that are randomised are analysed, and has been widely recommended as the preferred analysis strategy.[29] A modified intention-to-treat analysis excluding patients who died at each time point was also done and showed similar results (data not shown).

As an exploratory substudy, we also collected data from advance-care planning, end-of-life care, and quality of life near death. These data will be reported separately, as will data regarding caregiver-reported outcomes.

This randomised controlled trial has several strengths .First, it was adequately powered to detect a reliable effect on quality of life; the actual drop-out rate at 12 weeks was 5% less than expected. Second, patients were asked to complete two internationally well validated questionnaires [19,20] to measure quality of life enhancing the reliability of the results. The MQOL was added because of its high content and construct validity, and because it also addresses the existential aspects of quality of life.[30] Both instruments consistently showed improvements in quality of life, which adds to the robustness of our findings. Last, a detailed description of usual care was provided, which allows for an in-depth understanding of the effects of integrating early and systematic palliative care in oncology care.

Several limitations exist with regards to the design of this trial. First, it was a single-centre study in a tertiary university hospital setting, so the findings might not be generalisable to other settings. Second, a crossover effect cannot be excluded; staff members were not masked to patient allocation to the intervention or control groups. The treating oncologists and other members of the oncology team might have been affected by the intervention and have implemented insights gained from the early palliative care approach into the care of patients in the control group. Moreover, because the assessor was not masked, biased ascertainment of outcomes might have occurred. Third, selection bias might affect the results. Patients were informed about the study using the term palliative care, so it is likely that patients more open to palliative care participated in this trial. Fourth, because of the multi-component nature of the intervention, it is not possible to conclude which component has been effective. Additionally, as an exploratory study, many secondary endpoints were analysed and some reached significance by chance (type I error), which makes it difficult to draw firm conclusions. Fifth, we did not predefine by protocol an ESAS symptom assessment cut-off score to be use by palliative care nurses for patient referral to the palliative care physician. Sixth, we were not able to show a relationship between objective clinical parameters (eg, performance status and compliance with the intervention) because of homogeneity in performance status at baseline and data regarding the evolution of performance status were not collected prospectively. Last, adherence to the protocol was low; pre-specified

monthly consultations with the palliative care nurses and consultations every 3 months with the palliative care physician occurred less frequently.

In conclusion, in this trial early and systematic integration of palliative care into oncology care, as opposed to palliative care on demand, improved quality of life in our cohort. The findings of this trial provide additional, and more detailed insights into the effect of early and systematic integration of palliative care into oncology care. In the context of oncology care in Belgium, which focuses on alleviating psychosocial care needs by offering multidisciplinary psychosocial support as standard of care, this study shows that early and systematic palliative care can benefit patients with advanced cancer.

Contributors

All authors were involved in the design of the study and the figures, data interpretation, and writing of the article, and approved the final version of the manuscript. GV and KP did the literature search. GV, SVB, VS, MDL, KE, VC, and KG contributed to the data collection. GV, KP, RC, and LD analysed the data.

Declaration of interests

We declare no competing interests.

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References

1. Gaertner J, Wolf J, Ostgathe C, et al. Specifying WHO recommendation: moving toward disease-specific guidelines. *J Palliat Med* 2010; **13:** 1273–76.
2. Ferrell BR, Temel JS, Temin S, et al. Integration of palliative care into standard oncology care: American society of clinical oncology clinical practice guideline update. *J Clin Oncol* 2017; **35:** 96–112.
3. Greer JA, Jackson VA, Meier DE, Temel JS. Early integration of palliative care services with standard oncology care for patients with advanced cancer. *CA Cancer J Clin* 2013; **63:** 349–63.
4. Bauman JR, Temel JS. The integration of early palliative care with oncology care: the time has come for a new tradition. *J Natl Compr Cancer Netw* 2014; **12:** 1763–71.
5. Kavalieratos D, Corbelli J, Zhang D, et al. Association between palliative care and patient and caregiver outcomes: a systematic review and meta-analysis. *JAMA* 2016; **316:** 2104–14.
6. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010; **363:** 733–42.
7. Temel JS, Greer JA, El-Jawahri A, et al. Effects of early integrated palliative care in patients with lung and GI cancer: a randomized trial. *J Clin Oncol* 2017; **35:** 834–41.
8. Bakitas MA, Lyons KD, Hegel MT, et al. The project ENABLE II randomized controlled trial to improve palliative care for patients with advanced cancer. *J Am Med Assoc* 2009; **302:** 741–49.
9. Bakitas MA, Tosteson TD, Li Z, et al. Early versus delayed initiation of concurrent palliative oncology care: patient outcomes in the ENABLE III randomized controlled trial. *J Clin Oncol* 2015; **33:** 1438–45.
10. Zimmerman C, Swami N, Krzyzanowska M, et al. Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. *Lancet* 2014; **383:** 1721–30.
11. McClorke R, Sangchoon J, Ercolano E, et al. An advanced practice nurse coordinated multidisciplinary intervention for patients with late-stage cancer: a cluster randomized trial. *J Palliat Med* 2015; **18:** 962–69.
12. Maltoni M, Scarpi E, Dall'Agata M, et al. Systematic versus on-demand early palliative care: results from a multicentre, randomised clinical trial. *Eur J Cancer* 2016; **65:** 61–68.
13. Van Belle S. How to implement the multidisciplinary approach in prostate cancer management: the Belgian model. *BJU Int* 2008; **101** (suppl 2)**:** 2–4.
14. Lenaerts L, Remue E, Van Eycken L, Otter R, Van Hoof E. Evaluations of the cancer plan 2008–2010: results 2011. 2012. https://workspaces.wiv-isp.be/e-cancer/publicfiles/presentations/belgian_cancer_center/quantitative_evaluation_cancer_plan_results_2011_en.pdf (accessed March 15, 2017).
15. Federale Evaluatiecel Palliatieve Zorg. Evaluatierapport palliatieve zorg. 2014. http://leif.be/data/Wetgeving/Rapporten/ Evaluatierapport_palliatieve_zorg_2014.pdf (accessed Jan 21, 2018).

16. Beernaert K, Deliens L, Pardon K, et al. What are physicians' reasons for not referring people with life-limiting illnesses to specialist palliative care services? A nationwide survey. *PLoS One* 2015; **10:** e0137251.
17. Vanbutsele G, Van Belle S, De Laat M, et al. The systematic early integration of palliative care into multidisciplinary oncology care in the hospital setting (IPAC), a randomized controlled trial: the study protocol. *BMC Health Serv Res* 2015; **15:** 554.
18. Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. *J Palliat Care* 1991; **7:** 6–9.
19. Fayers P, Bottomley A. Quality of life research within the EORTC—the EORTC QLQ-C30. European Organisation for Research and Treatment of Cancer. *Eur J Cancer* 2002; **38:** 125–33.
20. Cohen SR, Mount BM, Bruera E, Provost M, Rowe J, Tong K. Validity of the McGill Quality of Life Questionnaire in the palliative care setting: a multi-centre Canadian study demonstrating the importance of the existential domain. *Palliat Med* 1997; **11:** 3–20.
21. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67:** 361–70.
22. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001; **16:** 606–13.
23. Manea L, Gilbody S, McMillan D. Optimal cut-off score for diagnosing depression with the patient health questionnaire (PHQ-9): a meta-analysis. *CMAJ* 2012; **184:** 191–96.
24. Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ* 1992; **305:**160–64.
25. Kristjanson LJ. Validity and reliability testing of the famcare scale: measuring family satisfaction with advanced cancer care. *Soc Sci Med* 1993; **36:** 693–701.
26. Deliens L, Mortier F, Bilsen J, et al. End-of-life decisions in medical practice in Flanders, Belgium: a nationwide survey. *Lancet* 2000; **356:** 1806–11.
27. Chambaere K, Vander Stichele R, Mortier F, Cohen J, Deliens L. Recent trends in euthanasia and other end-of-life practices in Belgium. *N Engl J Med* 2015; **372:** 1179–81.
28. Sullivan GM, Feinn R. Using effect size—or why the p-value is not enough. *J Grad Med Educ* 2012; **4:** 279–82.
29. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ* 2011; **343:** c869.
30. Albers G, Echteld MA, de Vet HC, Onwuteaka-Philipsen BD, van der Linden MH, Deliens L. Evaluation of quality-of-life measures for use in palliative care: a systematic review: *Palliat Med* 2010; **24:** 17–37.

Appendix: supplementary tables and figures

Figure 1.: Interview Form

Different topics:	**How much of the time have you discussed the topic?**
Illness understanding–Illness perception – Undertaken actions for eventual discomfort**:** _____ _____ _____ _____	**.....%**
Symptom management – (use of ESAS) Undertaken actions for eventual discomfort: _____ _____ _____ _____	.....%
Dealing with a life-threatening illness- psychological: Undertaken actions for eventual discomfort _____ _____ _____ _____	**.....%**
Dealing with a life-threatening illness – spiritual: Undertaken actions for eventual discomfort _____ _____ _____ _____	**.....%**
Support in eventual decision at the end-of-life: Undertaken actions for eventual discomfort _____ _____ _____ _____	**.....%**
Other topics Undertaken actions for eventual discomfort: _____ _____ _____	**.....%**

Table 1. Mean scores and differences (baseline adjusted) in symptom scales the EORTC QLQ-C30 at 12 weeks and 18 weeks.

	12 weeks					18 weeks					24 weeks				
	Mean score; Baseline adjusted (95% CI)		Difference (95% CI)	p value	Effect size	Mean score; Baseline adjusted (95% CI)		Difference (95% CI)	p value	Effect size	Mean score; Baseline adjusted (95% CI)		Difference (95% CI)	p value	Effect size
	Usual care (n=94)	Early and systematic palliative care (n=92)				Usual care (n=94)	Early and systematic palliative care (n=92)				Usual care (n=94)	Early and systematic palliative care (n=92)			
EORTC QLQ-C30 symptom scores															
Fatigue	47.03 (40.48 to 53.58)	40.48 (34.21 to 46.74)	-6.55 (-15.39 to 2.29)	0.14	-0.2	53.07 (45.27 to 60.88)	42.14 (34.63 to 49-67)	-10.93 (-21.30 to -0.57)	0.04	-0.4	48.31 (38.29 to 58.35)	39.85 (32.30 to 47.40)	-8.47 (-20.15 to 3.21)	0.15	-0.3
Nausea/ Vomiting	12.97 (7.91 to 18.02)	10.03 (5.17 to 14.89)	-2.93 (-9.78 to 3.91)	0.40	-0.1	13.35 (6.67 to 20.03)	15.20 (8.65 to 21.75)	1.85 (-7.19 to 10.90)	0.69	0.1	12.15 (3.49 to 20.81)	12.72 (6.42 to 19.02)	0.57 (-9.47 to 10.61)	0.91	0.0
Pain	28.19 (21.47 to 34.91)	23.18 (16.59 to 29.63)	-5.08 (-14.11 to 3.99)	0.27	-0.2	35.89 (26.07 to 45.71)	32.57 (22.73 to 42.40)	-3.32 (-15.89 to 9.25)	0.60	-0.1	38.59 (29.6 to 47.61)	31.55 (23.80 to 39.29)	-7.05 (-18.33 to 4.23)	0.22	-0.2
Dyspnoea	27.24 (20.14 to 34.34)	30.86 (24.05 to 37.67)	3.62 (-5.88 to 13.13)	0.45	-0.1	30.21 (22.27 to 38.15)	24.74 (17.00 to 32.49)	-5.47 (-16.13 to 5.19)	0.32	-0.2	28.48 (19.65 to 37.31)	24.55 (17.65 to 31.44)	-3.92 (-14.45 to 6.60)	0.46	-0.1
Insomnia	30.14 (22.84 to 37.44)	21.34 (13.91 to 28.76)	-8.80 (-19.27 to 1.67)	0.10	-0.3	30.41 (22.14 to 38.67)	24.17 (16.13 to 32.22)	-6.23 (-17.41 to 4.95)	0.27	-0.2	30.34 (20.08 to 40,60)	20.16 (11.48 to 28.85)	-10.17 (-22.65 to 2.30)	0.11	-0.3
Appetite loss	25.83 (17.69 to 33.97)	20.70 (12.93 to 28.48)	-5.13 (-16.26 to 6.00)	0.36	-0.1	27.75 (17.88 to 37.63)	23.91 (14.32 to 33.50)	-3.83 (-17.29 to 9.62)	0.57	-0.1	24.20 (14.19 to 34.21)	21.00 (12.61 to 29.40)	-3.20 (-16.06 to 9.67)	0.62	-0.1
Constipation	19.54 (12.69 to 26.39)	14.25 (7.51 to 21.00)	-5.29 (-14.59 to 4.01)	0.26	-0.2	24.73 (15.92 to 33.51)	14.81 (6.45 to 23.16)	-9.93 (-21.57 to 1.72)	0.09	-0.3	30.21 (20.96 to 39.47)	14.53 (6.86 to 22.21)	-15.68 (-27.05 to -4.31)	0.007	-0.5
Diarrhoea	9.07 (3.93 to 14.22)	10.15 (5.20 to 15.09)	1.07 (-5.72 to 7.88)	0.75	0.0	6.67 (-0.71 to 14.05)	17.11 (10.63 to 23.58)	10.44 (1.62 to 19.25)	0.02	0.4	13.10 (3.72 to 22.49)	13.44 (6.29 to 20.58)	0.33 (-11.22 to 11.89)	0.95	0.0
Financial problems	15.61 (10.46 to 20.77)	13.92 (8.69 to 19.15)	-1.69 (-8.74 to 5.35)	0.63	-0.1	18.25 (10.31 to 26.18)	15.10 (7.55 to 22.66)	-3.15 (-13.46 to 7.16)	0.55	-0.2	15.84 (6.59 to 25.09)	14.95 (8.37 to 21.53)	-0.89 (-11.39 to 9.61)	0.87	0.0

Higher mean scores represent a higher symptoms. Imputations (n=50) with predictors: age, sex, department, ECOG performance status, group, treatment, tumour site, and days between diagnosis and baseline. $p<0.05$ indicates significance. EORTC QLQ-C30= European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire version 30.

Table 2. Sensitivity analysis for all significant results based on complete case analysis and modified intention-to-treat for quality of life at 12, 18 weeks and 24 weeks.

Complete cases	12 weeks		18 weeks		24 weeks	
	Difference (95% CI) (n= 130)[a]	p-value	Difference (95% CI) (n=105)[b]	p-value	Difference (95% CI) (n=94)[c]	p-value
Quality-of-life summary scores						
EORTC QLQ-C30 global health status/QOL scale (primary outcome)	-7.4 (-13.83 to -.93)	0.03	-7.5 (-13.90 to -1.08)	0.02	-4.7 (-13.23 to 3.86)	0.28
MQOL Single Item Scale	-1.10 (-1.71 to -0.48)	0.001	-1.16 (-1.83 to -0.49)	0.001	-0.53 (-1.34 to 0.27)	0.19
Functioning scores						
Physical functioning (EORTC QLQ-C30)	-6.01 (-12.86 to 0.85)	0.09	-10.27 (-17.96 to -2.59)	0.01	-11.3 (-19.50 to -3.1)	0.008
Role functioning (EORTC QLQ C30)	-9.53 (-18.59 to -0.47)	0.04	-14.59 (-25.94 to -3.23)	0.01	-6.9 (-18.3 to 4.6)	0.24
Existential Scale (MQOL)	-0.69 (-1.22 to -0.16)	0.01	-0.42 (-1.04 to 0.19)	0.18	-0.51 (-1.16 to 0.14)	0.12
EORTC QLQ-C30 symptom scores						
Fatigue	6.95 (-1.18 to 15.08)	0.09	11.58 (2.71 to 20.44)	0.01	8.9 (0.84 to 18.7)	0.07
Diarrhoea	-0.75 (-6.97 to 5.46)	0.81	-7.99 (-15.96 to -0.02)	0.05	1.55 (-7.7 to 10.8)	0.74

a. Twenty-three patients died by 12 weeks, missings N= 33, b. Thirthy-three patients died by 18 weeks, missing N= 48, c. Forthy-seven patients died by 24 weeks, missing N= 45. $p<0.05$ indicates significance. EORTC QLQ-C30= European Organisation for research and Treatment of Cancer Quality of Life Questionnaire version 30. MQOL=McGill Quality of Life Questionnaire.

Table 3: Mood at 12, 18, and 24 weeks.

Mood	12 weeks Early and systematic PC (vs. Usual Care) OR (95% CI)	p-value	18 weeks Early and systematic PC (vs. Usual Care) OR (95% CI)	p-value	24 weeks Early and systematic PC (vs. Usual Care) OR (95% CI)	p-value
HADS						
Depression *(vs no depression)*	0.59 (0.27 to 1.29)	0.18	0.75 (0.33 to 1.70)	0.49	0.41 (0.15 to 1.11)	0.08
Anxiety *(vs no anxiety)*	0.80 (0.36 to 1.77)	0.59	0.58 (0.22 to 1.51)	0.26	0.71 (0.28 to 1.81)	0.47
PHQ-9 Depression[b]						
Depression *(vs no depression)*	0.70 (0.31 to 1.58)	0.39	1.13 (0.42 to 3.04)	0.81	063 (0.18 to 2.16)	0.46

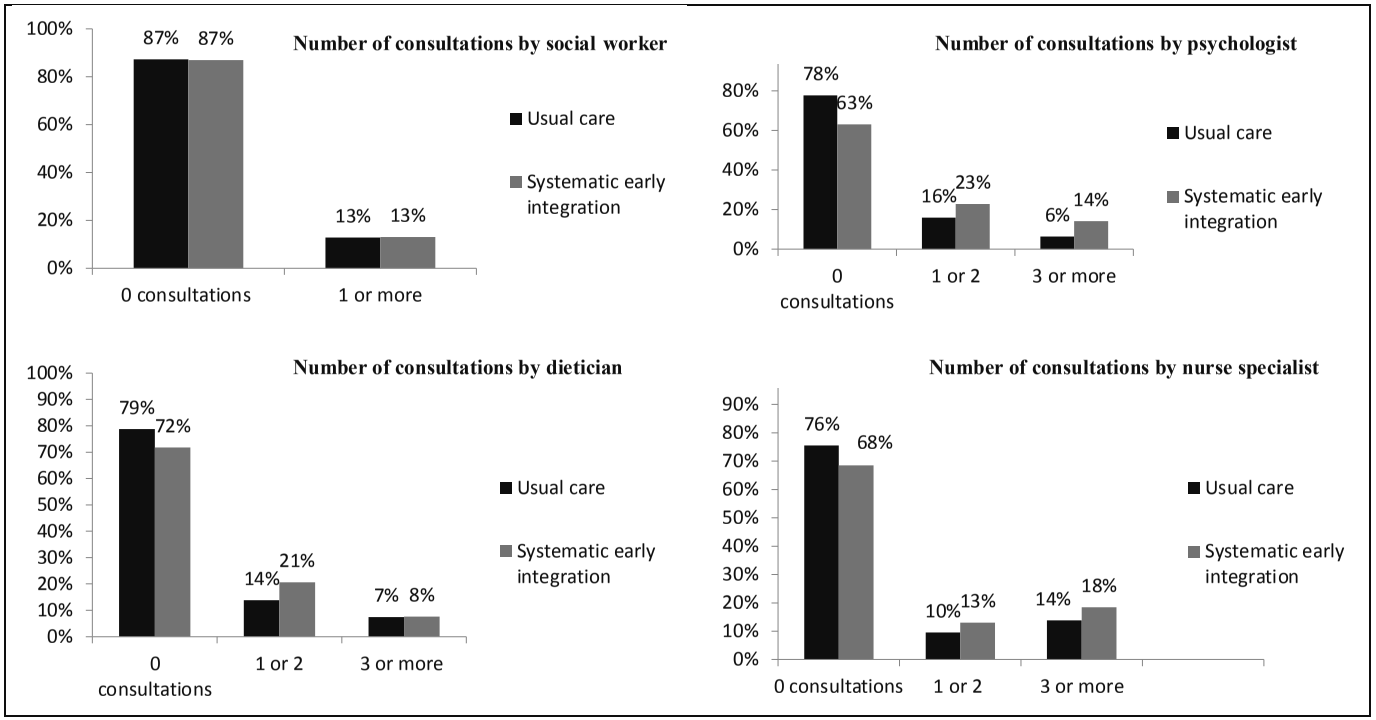
[a] *Cut-off score > 7,* [b] *Cut-off score ≥ 8.* $p<0.05$ indicates significance. HADS= the Hospital Anxiety And Depression Scale. PHQ-9= the Patient Health Questionnaire.

Table 4: Illness understanding at 12, 18, and 24 weeks.

	12 weeks		18 weeks		24 weeks	
Illness understanding	**Early and systematic PC (vs. Usual Care) OR (95% CI)**	**p-value**	**Early and systematic PC (vs. Usual Care) OR (95% CI)**	**p-value**	**Early and systematic PC (vs. Usual Care) OR (95% CI)**	**p-value**
Perception of goals of therapy		0.03		0.76		0.53
To try to make me feel better	3.70		1.14		1.89	
(vs. to help me live longer)	(1.33 to 10.29)		(0.44 to 2.98)		(0.61 to 5.83)	
To get rid of my cancer)	2.23		1.51		1.76	
(vs. to help me live longer)	(0.73 to 6.82)		(0.49 to 4.62)		(0.42 to 7.35)	
Health perception		0.84		0.99		0.50
Relatively healthy	0.78		1.06		1.61	
(vs. seriously ill and terminally ill)	(0.33 to 1.83)		(0.42 to 2.68)		(0.61 to 4.25)	
Seriously ill but not terminally ill	0.95		1.05		1.90	
(vs. seriously ill and terminally ill)	(0.35 to 2.55)		(0.39 to 2.83)		(0.54 to 6.65	
Understanding of prognosis		0.51		0.36		0.53
Curable	1.37		1.45		1.53	
(vs Incurable)	(0.54 to 3.48)		(0.50 to 4.24)		(0.40 to 5.88)	

For patients who ticked off more than one goal of therapy, to get rid of my cancer prevailed over helping me to live longer and over trying to make me feel better while helping me to live longer prevailed over trying to make me feel better. . $p<0.05$ indicates significance.

Figure 2. Number of consultations by the multidisciplinary medical team by 18 weeks (in percentages).



Chapter 6:

Early and systematic integration of palliative care in multidisciplinary oncology care: the effect on informal carers.

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Submitted

Abstract

Background: We evaluated if early and systematic integration of palliative care (PC) in oncology care that benefits patients with advanced cancer, compared to usual care, also has an impact on informal carers.

Patients and Methods: We randomly assigned advanced cancer patients with a life-expectancy of one year and their informal carers to early and systematic integration of PC into oncological care (n=60) or usual care (n=55). Eligible carers lived with or had in-person contact with the patient at least twice a week and were likely to accompany him/her to the hospital. Carers completed validated measures assessing quality of life [SF-36v2 Health Survey], satisfaction with care [FAMCARE], mood [Hospital Anxiety and Depression Scale (HADS)] at baseline, 12 weeks, and six weekly thereafter until death.

Results: Carers from the intervention group (versus usual care) reported greater improvements in the mental component score (MCS) of the SF36v2 Health Survey at 18 weeks. No significant improvements were found in the physical component score (PCS) (12 weeks: P=0.21, 18 weeks: P = 0.02) or MCS (P= 0.44) at 12 weeks. No significant differences were found in the HADS depression subscale (12 weeks; P=0.34; 18 weeks; P=0.38), HADS anxiety subscale (12 weeks; P=0.73; 18 weeks; P=0.90) or in overall satisfaction with care (12 weeks; P=0.88; 18 weeks; P=0.73). A terminal decline analysis showed significant intervention effects on carers QOL, with effects at one (PCS: P= 0.02 , MCS: P= <0.001), three (PCS: P=0.02 , MCS: P= 0.002), and six (PCS: P=0.02 , MCS: P=0.02) months before patient death.

Conclusion: Early integration of palliative care in oncology care improves the quality of life of informal carers of patients with advanced cancer, soon after diagnosis and close to the patient's death.

Introduction

Patients with advanced cancer experience high symptom burden, due to their progressing disease and the toxicities of treatment which results in complex support and care needs [1]. They are, however, more and more often treated in the outpatient setting which leads to increasing caregiving requirements for informal carers. Family carers and friends often are poorly prepared and have little knowledge on how to fulfil these complex needs [2]. Research shows that providing care for cancer patients negatively influences emotional well-being, physical health and overall quality of life (QOL) of carer's [3–6]. It also demonstrates that carers of palliative care patients report lower quality of life than carers caring for patients in the curative phase [7].

Improving QOL and reducing suffering of patients with a life-threatening disease as well as that of their family carers have been recognized as central goals of palliative care [8]. Recent studies have consistently shown the benefits of early PC on patient-reported outcomes such as QOL and mood shortly after diagnosis of advanced disease [9–13]. However, only three trials worldwide have examined the effect of early PC on wellbeing of carers of patients with advanced cancer.[16–18] It was shown that early PC positively influenced satisfaction with care and decreased depressive symptoms of carers in the short term as well as closer to the patient's death. None of these studies found an effect on QOL of informal carers, the primary aim of palliative care.

All three trials have been conducted in North America and evidence from Europe is lacking. We conducted a randomized controlled trial of early and systematic palliative care integrated in oncology care compared to usual care in patients with advanced cancer. We have reported primary and secondary outcomes for patients elsewhere, this included improved the QOL of patients even when they are already standardly offered multidisciplinary psychosocial support in usual care [14]. Here we report our outcomes of the informal carers. We hypothesize that carers randomly assigned to early and systematic integration of palliative care will report better quality of life compared to carers assigned to usual oncology care.

Methods

Study design

We conducted a non-blinded randomized controlled trial (RCT) in which patients with advanced cancer were randomly assigned together with their carers to either early and systematic integration of palliative care into usual oncology care (intervention) or usual oncology care alone (control). The Ethical Committee of the University Hospital Ghent approved the study protocol. The full protocol of the study has been published elsewhere [19].

Participants and settings

From 29 April 2013 to 29 February 2016, patients with advanced cancer and their carers were recruited from the Medical, Thoracic and Digestive Oncology departments of the Ghent University Hospital in Belgium.

Patients were eligible if they (1) were diagnosed with advanced solid tumour cancer and were within 12 weeks of a new diagnosis or of an illness progression. Patients originating from a hospital other than the Ghent University Hospital were required to be within 12 weeks of receiving first-line treatment or of a progression, (2) had a life expectancy of approximately one year (assessed by the treating oncologist) (3) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2, and (4) were able to read and respond to questions in Dutch. Patients were excluded if they were under 18 years old, were cognitively impaired or had had more than one PC consultation since the onset of the disease or one PC consultation in the six months prior to the new diagnosis or progression.

Upon enrolment, patients were asked to identify an informal carer who would be invited to participate in the study. Patients were asked to identify a carer that should either live with or have in-person contact with him or her at least twice a week and who would likely accompany them to the hospital. Patients who did not have a carer were not excluded from the trial. A well trained clinical research assistant attended the weekly staff meetings to identify patients together with the treating oncologists. The research assistant approached carers for participation in the study after consent of the patients. Patients and carers provided written informed consent.

Randomization and masking

Patients and carers were randomly assigned as dyads in a 1:1 ratio to either systematic early integration of palliative care in oncological care (intervention group) or to usual oncological care (control group). A randomized block design, stratified by treating department was applied. Computer-generated sequences were created by a statistician, the allocation sequence was only available to an independent administrative assistant and was kept unknown to the investigators. The research assistant enrolled the patients and carers and called the administrative assistant to obtain a patient study number and the corresponding allocation. Masking those giving the intervention, those assessing the outcomes and those analyzing the data was not possible.

Procedures

The intervention group received early and systematic palliative care alongside usual oncology care and met with a palliative care nurse from the PC team of the hospital within three weeks of enrolment and monthly thereafter. The intervention was primarily patient-centered, topics such as illness understanding, symptom burden, support in decision making, and support for emotional, social and/or spiritual needs were discussed in the consultations. Carers were motivated to be present during consultations and when present they were encouraged by the PC nurses to participate in the conversation. . The PC physician visited patients on referral from the PC nurse. A detailed description of the intervention and the main areas of focus of the intervention were reported elsewhere [14]. The control group received usual oncology care provided by oncologists, psychologists, social care nurses, dieticians and nurse specialists. In usual oncology care, the palliative care team was only involved in the care of the patients on demand.

Data collection and instruments

Questionnaires were administered at baseline, 12 and 18 weeks and six weekly thereafter until the participant patient's death or study completion. An additional questionnaire was send 3 months after the patient's death.

Demographic questionnaire

Carers were asked to indicate their gender, age, education and employment status, marital status, religion, family composition, relationship to the patient (e.g., spouse or friend) and length of the relationship to the patient at baseline.

Quality of life

As a measure of general quality of life, the Medical Health Outcomes Survey- Short Form (SF-36) was used. This 36-item self-report measure assesses eight domains of health-related quality of life. Response scores are scored into eight scales: physical functioning, role limitation due to physical health problems, bodily pain, general health, vitality, social functioning and role limitation due to emotional/mental health[20]. The scales are aggregated, into two summary scores: physical (PCS) and mental component score (MCS) (MCS) [21,22]. These summary scales are T-transformed, so that in a US norm population the mean of the summary scale scores is 50, and one standard deviation (SD) is 10 points. A minimal clinically difference of 3-5 points has been reported [23]. The SF-36 has been used as an outcome measure in randomized controlled trials with family carers involvement[16,18].

Mood

Mood of the carers was measured by the Hospital Anxiety and Depression Scale (HADS). It is a self-assessment scale (14 items) that consists of two subscales that assess anxiety and depression symptoms with subscale scores range from 0 to 21 (maximum distress).

Satisfaction with care and illness understanding

The carer's satisfaction with care was assessed with the use of the 20-item FAMCARE. This is a well-validated questionnaire that has been used in several recent studies evaluating family carer satisfaction with palliative care [24,25]. It is a 20 item Likert-type scale measuring the degree to which family members are satisfied with the care provided to them and the patients [24]. The FAMCARE includes four subscales: information giving, physical patient care, psychosocial care, and availability of care. Illness understanding by carers was measured [9] based on the forward-backward translation of the questionnaire used in the Temel study containing questions regarding prognosis of the disease of the patient(curable versus non-curable), the goals of therapy (to help the patient live longer, to try to make them feel better or to get rid of/cure their cancer) and health perception of the disease of the patient (relatively healthy, seriously but not terminally ill, or seriously and terminally ill).

Statistical analysis

The primary outcome of our trial was patient's quality of life and the study was powered on this outcome, resulting in a sample size of 182 patients with advanced cancer. Carers were included until we achieved the patient sample size. We performed statistical analysis using SPSS software (version 24), SAS software (version 9.4) and R (version 3.4.1). Data obtained April 29 2013 to November 8 2017 were included. In our analyses, the data of patients without a carer participating in the trial were excluded. All carers and patients were analyzed according to their original randomization, following the intention to treat principle. Multiple imputation (n=50) for missing data was applied using the fully conditional specification (FCS) method of the multiple imputation procedure in SAS. The predictors of the imputation model were the carer's age and gender and the patient's ECOG performance status and treating department. A linear regression model with score at baseline, group and department as predictor variables was applied on the imputed dataset using the MIANALYZE procedure to assess the effect of early and systematic PC on quality of life, mood, and satisfaction with care. A sensitivity analysis was done for handling missing data by using complete case analysis. A terminal decline joint model was applied that models carer's QOL backward from the time of the patient's death rather than prospectively from the time of enrolment[26]. This approach controls for the known relationship between the deterioration in patient's and carer's QOL as the patient's death is nearing. This is

a recent technique that has the advantage of considering the dependence between patient- and carer QOL and patients 'survival while accounting for missing data and is often used in early palliative care trials. It combines two sub-models to analyze both the terminal trend of the outcome scores of QOL (PCS and MCS) and the survival outcomes The first sub-model is a semi-parametric mixed effects model to compare the longitudinal trend of the outcome scores between groups, including variables department (the stratification factor) and the baseline scores as covariates. The second sub-model is a Cox model comparing the survival outcomes between groups correcting for department. The knots were selected based on Akaike information criterion (AIC). All analyses were applied using R code made available by the authors Li et al. [26] For each time point of interest (one, three and six months prior to death), a model-based 95% confidence interval for the mean outcome score is presented. Only the carers for which a baseline measurement was available (n=113) were included in the terminal decline analysis. For the outcome illness understanding, a logistic regression analysis was applied on the complete cases adjusting for the stratification factor. This trial is registered with ClinicalTrials.gov, number NCT01865396.

Results

Baseline characteristics

From April 29, 2013 to February 29, 2016, we enrolled 186 patients and 115 (61.8%) patients identified an informal carer that was included in the study. The median age of the carers was 61 years (interquartile range (IQR): 52.3-68.4), 79 of 115 (69%) were female and 79% (91/115) were married or partner of the patient. Results from screening, eligibility and randomization are presented in Figure 1. Fifty-five (48%) of 115 patients were assigned to early and systematic PC and 60 (54 %) to usual care. The baseline characteristics of the carers are shown in Table 1. At 12 and 18 weeks, the response rate was 72% (83 of 115 questionnaires) and 57% (66 of 115 questionnaires) respectively. Fifty-one patients (93%) in the intervention arm attended at least one palliative care consultation (median 5; interquartile range (IQR) 2- 12), 25 control patients (42%) received at least one palliative care consultation (median 0; IQR 0-1.8) within the trial period. By November 8, 2017 (time of analysis), 78% (90 of 115) of patients with an informal carer had died.

Figure 1: Trial Profile

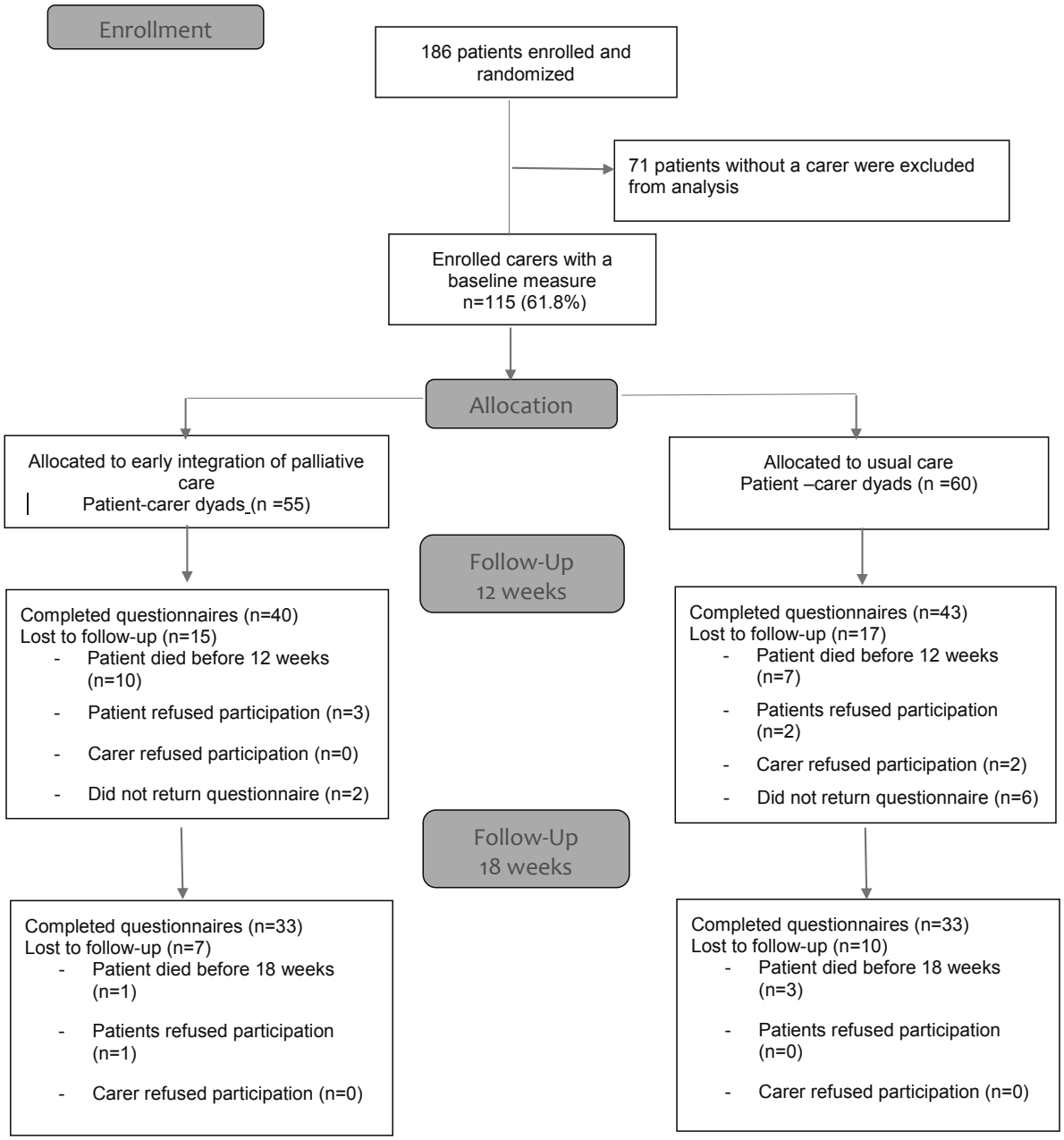

Table 1. Baseline characteristics of informal carers and patients.

Variable	Usual Care (n=60)	Early and systematic PC (n=55)
Characteristics of informal carers		
Age- median (IQR[a])	61.1 (51.4-68.4)	59.0 (52.0-67.2)
Women - no (%)	39 (66)	39 (71)
Married no (%)	53 (90)	52 (95)
Years known patient median (IQR)+	42.0 (31.0-53.0)	40.0 (30.0-49.3)
Relationship with patient - no (%)		
Wife/Husband/Partner	50 (85)	40(76)
Son/daughter	6 (10)	7 (13)
Friend	0 (0)	4 (8)
Other family member[b]	3 (5)	2 (4)
Education - no (%)		
Less than high school	7 (12)	3 (6)
Lower level in high school	10 (17)	8 (15)
Higher level in high school	22 (37)	17 (31)
College, university, or other	20 (33)	27 (49)
Quality of Life at baseline		
SF-36 PCS[c], mean (95%CI)	34.8 (32.8; 36.8)	36.4 (34.7; 38.1)
SF-36 MCS[d], mean (95% CI)	40.0 (37.4; 42.6)	40.6 (38.1; 43.0)
Satisfaction with care at baseline		
FAMCARE[e], mean (95% CI)	80.6 (77.2, 83.9)	78.3 (75.1, 81.5)
Mood at baseline		
HADS-Depression[f], mean (95%CI)	5.9 (4.8, 7.0)	5.6 (4.5, 6.8)
HADS-Anxiety[g], mean (95%CI)	8.7 (7.4, 10.0)	8.2 (7.1, 9.2)
Characteristics of patients [h]		
Medical department - no (%)		
Digestive Oncology	19 (32)	22 (39)
Medical Oncology	24 (40)	16 (29)
Thoracic Oncology	16 (27)	18 (32)
Patient ECOG[i] performance status - no (%)		
0 - the patient is asymptomatic	16 (27)	24(43)
1 - the patient is symptomatic but fully ambulatory	33 (55)	25 (45)
2 - the patient is symptomatic and in bed less than 50% of the day	6 (10)	6 (11)
3 - the patient is capable of only limited self-care, confined to bed or chair more than 50% of waking hour[j]	4 (7)	1 (2)
Tumour Site - no (%)		
Gastrointestinal	19 (32)	22 (39)
Lung	16 (27)	18 (32)
Head & Neck	9 (15)	2 (4)
Breast	3 (5)	3 (5)
Melanoma	7 (12)	4 (7)
Genitourinary	5 (8)	7 (13)

a. Interquartile range (IQR)
b. Other family members includes sister, son-in-law and daughter-in law
c. The SF-36 PCS (Physical Component Summary of the SF-36v2 Health Survey) ranges from 12 to 46, with higher numbers indicating better health (functioning).

d. The SF-36 MCS (Mental Component Summary of the SF-36v2 Health Survey;) ranges from 18 to 59, with higher numbers indicating better health (functioning).
e. The 20-item FAMCARE caregiver satisfaction with care scale (minimum 0; maximum 100) ranges from 38 to 100, with higher numbers representing better caregiver satisfaction
f. The HADS depression (Depression scale of the HADS; minimum 0; maximum 21) ranges from 0 to 17, with higher number indicating higher distress.
g. The HADS anxiety (Depression scale of the HADS; minimum 0; maximum 21) ranges from 1 to 20, with higher number indicating higher distress.
h. Patients of whom an informal carer didn't participate in the study were excluded (n=71).
i. *ECOG denotes Eastern Cooperative Oncology Group* and was assessed by the treating physician
j. At screening, all patients with ECOG performance status ≤2 were selected, five patients deteriorated to ECOG performance status of 3 at baseline; these patients were not excluded from analysis .

Quality of life

At week 12, we observed no significant intervention effects on informal carer's physical component score (PCS) or mental component score (MCS) of QOL, measured by the SF-36. At 18 weeks, early and systematic PC had a significantly positive effect on the MCS (adjusted mean difference: 4.2 [95% CI 0.5- 7.9], p=0.03) but not on the PCS (adjusted mean difference: 1.1 [0.8- 8.6], p= 0.67). See Table 2. When applying the terminal decline model, carers in the intervention group scored significantly higher on the physical component score at six (difference: 2.2 [0.29; 4.1], p=0.02), three (difference: 2.3 [0.33; 4.35], p=0.02) and one month (difference: 2.4 [0.33; 4.52], p=0.02) prior to the patient's death compared to the control group. The carers in the intervention group also scored higher on the mental component score at six (difference: 3.5 [0.48; 6.54], p=0.02), three (difference: 4.6 [1.74; 7.49], p=0.002) and one month (difference: 6.1 [2.67; 9.59], p= < 0.001) prior to the patient's death. See Figure 2.

Mood, satisfaction with care and illness understanding

No effects were found on depression subscale or anxiety subscale measured by the HADS. At 12 and 18 weeks, no effects were found on overall satisfaction with care or on the subscales information giving, physical patient care, psychosocial care or availability of care (see Table 2). The sensitivity analysis showed similar results (See Table 3). The carer his or her perceptions of the goals of therapy of their relatives, their understanding of the relative's prognosis and perception of the overall health of the relatives did not differ significantly between both groups at 12 or 18 weeks (See Table 4).

Table 2. Mean scores and differences (baseline adjusted) in informal carer's quality of life, satisfaction with care and mood at 12 and 18 weeks from baseline.

	12 weeks				18 weeks			
	Usual care	Early and systematic integration of PC			Usual care	Early and systematic integration of PC		
	Mean score; Baseline adjusted (95% CI)	Mean score; Baseline adjusted (95% CI)	Difference between intervention group and control group, baseline adjusted (95% CI)	p-value	Mean score; Baseline adjusted (95% CI)	Mean score; Baseline adjusted (95% CI)	Difference between intervention group and control group, baseline adjusted (95% CI)	p-value
Quality of Life	*Higher score means better quality of life*							
SF-36 Physical Component	34.0 (32.4; 35.7)	35.6 (33.9; 37.2)	1.5 (-0.9; 3.9)	0.21	33.7 (31.7; 35.7)	36.1 (34.1; 38.1)	2.4 (-0.5; 5.3)	0.10
SF-36 Mental Component	39.9 (37.5; 42.3)	41.3 (38.9; 43.6)	1.4 (-2.4; 4.9)	0.44	38.9 (36.3; 41.5)	43.1 (40.5; 45.7)	4.2 (0.5; 7.9)	**0.03**
Satisfaction with care (FAMCARE)	*Higher score means better satisfaction with care*							
Overall satisfaction with care	80.1 (76.6; 83.6)	79.8 (76.5; 83.0)	-0.4 (-5.4; 4.6)	0.88	74.7(70.0; 79.4)	75.8 (71.5; 80.2)	1.2 (-5.6; 8.0)	0.73
Availability of care	81.0 (76.0-86.0)	80.9 (76.3; 85.4)	-0.1 (-7.3; 7.1)	0.97	76.6 (71.4; 81.9)	75.8 (71.2; 80.5)	-0.8 (-8.1; 6.4)	0.82
Information giving	79.4 (75.5; 83.4)	78.4 (74.7; 82.0)	-1..0 (-6.5; 4.5)	0.71	74.6 (68.9; 80.3)	75.1 (69.3; 80.9)	0.44 (-8.0; 8.9)	0.92
Psychosocial care	78.2 (74.2; 82.2)	77.4 (73.3; 81.6)	-0.7(-6.8; 5.3)	0.80	72.6 (66.9; 78.3)	73.2 (67.8; 78.5)	0.59 (-7.6; 8.8)	0.89
Physical care	81.2 (77.5; 85.0)	81.9 (78.3; 85.5)	0.6 (-4.7; 6.0)	0.81	75.7 (70.9; 80.7)	77.9 (73.5; 82.3)	2.1(-4.5; 8.7)	0.53
Mood	*Higher score means more distress*							
HADS depression	6.2 (5.1; 7.4)	5.5 (4.4; 6.6)	-0.8 (-2.4; 0.9)	0.34	6.7 (5.1; 8.4)	5.7 (4.0; 7.3)	-1.1(-3.5; 1.4)	0.38
HADS anxiety	8.0 (6.8; 9.2)	7.7 (6.7; 8.8)	-0.3 (-1.8; 1.3)	0.73	8.2 (6.6; 9.7)	8.3 (6.9; 9.7)	-0.1 (-1.9; 2.2)	0.90

Figure 2: Evolution of physical component and mental component of informal carer QOL at six, three and one month prior to death.

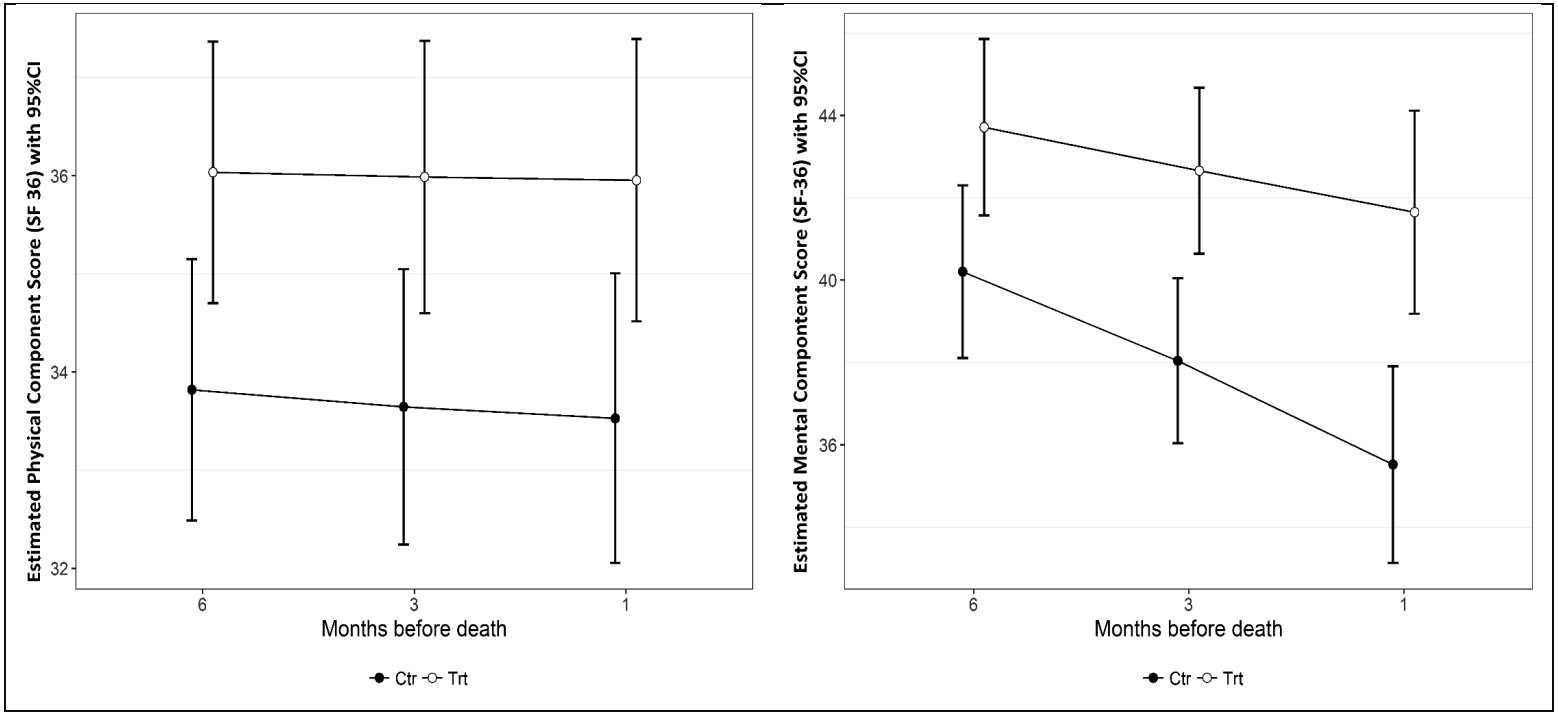

Table 3. Sensitivity analysis of informal carer's quality of life, satisfaction with care and mood at 12 and 18 weeks

	12 weeks				18 weeks			
	Usual care	Early and systematic integration of PC			Usual care	Early and systematic integration of PC		
	Mean score; Baseline adjusted (95% CI)	Mean score; Baseline adjusted (95% CI)	Difference between intervention group and control group, baseline adjusted (95% CI)	**p-value**	Mean score; Baseline adjusted (95% CI)	Mean score; Baseline adjusted (95% CI)	Difference between intervention group and control group, baseline adjusted (95% CI)	**p-value**
Quality of Life	*Higher score means higher quality of life*							
SF-36 Physical Component	34.3(32.6; 36.0)	35.5 (33.9; 37.1)	1.8 (1.2; 3.5)	0.30	34.0 (32.1; 35.9)	36.3 (34.5; 38.1)	2.3 (-0.3; 4.9)	0.08
SF-36 Mental Component	40.2 (37.8; 42.6)	40.7 (38.4; 43.0)	0.5 (-2.8; 3.9)	0.80	39.2 (36.7; 41.6)	43.3 (41.1; 45.6)	4.2 (0.9; 7.5)	**0.02**
Satisfaction with care FAMCARE	*Higher score means higher satisfaction with care*							
Overall satisfaction with care	80.3 (76.9; 83.7)	79.4 (76.1; 82,7)	-0.9 (-5.6; 3.9)	0.71	75.4 (70.8; 80.1)	76.6 (72.2; 81.1)	1.2 (-5.2; 7.6)	0.701
Availability of care	81.1 (76.6; 85.6)	80.0 (75.5; 84.4)	-1.1 (-7.4; 5.3)	0.70	77.4 (72.5; 82.4)	75.3 (70.4; 80.2)	-2.2 (-9.1; 4.8)	0.50
Information giving	79.2 (75.4; 83.0)	77.6 (73.8; 81.3)	-1.6 (-7.0; 3.8)	0.60	74.9 (69.1; 80.9)	75.4 (69.8; 81.1)	0.5 (-7.6; 8.6)	0.90
Psychosocial care	78.3 (74.1; 82.6)	77.1 (73.1; 81.2)	-1.3 (-7.1; 4.6)	0.70	73.7 (67.9; 79.6)	74.4 (68.8; 80.0)	0.7 (-7.4; 8.8)	0.90
Physical care	81.5 (77.8; 85.2)	81.9 (78.3; 85.5)	0.4 (-4.7; 5.6)	0.90	76.5 (72.2; 80.9)	79.0 (74.8; 83.2)	2.5 (-3.6; 8.5)	0.40
Mood	*Higher score means higher distress*							
HADS depression	6.4 (5.2; 7.6)	5.7 (4.6; 6.9)	-0.7 (-2.3; 0.9)	0.41	6.5 (4.9; 8.1)	5.4 (3.8; 6.9)	-1.1 (-3.3; 1.1)	0.33
HADS anxiety	7.7 (6.6; 8.9)	7.7 (6.6; 8.8)	-0.03 (-1.6; 1.5)	0.97	7.9 (6.5; 9.2)	7.7 (6.5; 9.0)	-0.1 (-2.0; 1.7)	0.89

Table 4: **Illness understanding at 12 and 18 weeks.**

Illness understanding	12 weeks			18 weeks		
	Early and systematic PC (vs. Usual Care) OR (95% CI)	P-value	N	Early and systematic PC (vs. Usual Care) OR (95% CI)	P-value	N
Perception of goals of therapy		0.7	52		0.3	39
To help my relative to live longer *(vs To get rid of/cure his or her cancer)*	0.5 (0.1-2.8)			0.3 (0.1-1.5)		
To try to make my relative feel better *(vs To get rid of/cure his or her cancer.)*	0.7 (0.2-2.8)			0.5 (0.1-2.7)		
Health perception		0.5	81		0.6	63
Relatively healthy *(vs. seriously ill and terminally ill)*	1.8 (0.6-5.3)			1.0 (0.3-3.5)		
Seriously ill but not terminally ill *(vs. seriously ill and terminally ill)*	0.8 (0.3-2.6)			0.4 (0.1-2.1)		
Understanding of prognosis		0.3	83		0.6	62
Curable *(vs Incurable)*	2.0 (0.5-9.2)			1.6 (0.2-10.6)		

a. For caregivers who ticked off more than one goal of therapy, to get rid of my relative's cancer prevailed over helping my relative to live longer and over trying to make my relative feel better while helping my relative to live longer prevailed over trying to make my relative feel better.

Discussion

This trial is the first to show that early and systematic integration of palliative care in usual care does not only improve the quality of life of patients with advanced cancer[14], but also the quality of life of their informal carers. After 18 weeks, the informal carers of patients assigned to early and systematic integration of palliative care reported a statistical and clinically relevant improvement in the mental component of QOL compared with carers of patients receiving usual care. Carers in the intervention arm also reported higher mental as well as physical QOL in the months closer to the patient's death. These findings are an important contribution to the literature since the primary aim of any palliative care approach is to improve the QOL of patients with serious illness as well as that of their families.[8]

This is to our knowledge the first time that a trial of early integration of palliative care in oncological care demonstrates favorable effects on the quality of life of informal carers of patients with advanced cancer. We found an effect on the carer's QOL by providing monthly semi-structured PC consultations that allowed for an individual approach with patients and carers. The consultation focused on aspects such as illness understanding, symptom burden, and support for emotional and social needs to patients and their informal carers early in the disease trajectory of patient with advanced cancer. The intervention was offered to both patients and their informal carers, allowing both individuals to have their questions answered and to hear the concerns of their partner [27]. This complex intervention doesn't allow to make conclusions regarding the mechanisms of early palliative care for patients or for carers. However, the beneficial effect of early PC on informal carer's QOL might be related to the increased information and support that is offered to the patients and their carers. It is known that carers value care that is coordinated, personalized and holistic care[16,27] and that social support accounts for a significant amount of variance in carers quality of life [28]. Additionally, the benefits of early and systematic palliative care on the QOL of patients may also be a plausible mechanism of the favorable effects on the QOL of carers. Carers have reported that their own QOL is strongly influenced by the wellbeing and quality of life of the patient.[29,30]. This indicates that early palliative care interventions at the level of the patient might also benefit the carer indirectly.

Interestingly, early and systematic integration of early PC resulted in a statistically and clinically higher score on the mental component of QOL at 18 weeks and in six months, three months and one month prior the time of death of patients. The absence of a significant difference at 12 weeks in combination with the positive effects in the long term may indicate a delayed effect of early PC on carer's mental QOL. This is in line with a recent meta-analysis of interventions with carers of patient with cancer that reported delayed effects on caregiver benefit and social functioning. It is stated that this may be because of the additional time required for carers to make the necessary changes such as reframing and refocusing their life and relationships [30,31].

Unlike the mental component of QOL, early and systematic integration of palliative care in oncology did not significantly improve the carers' physical aspect of QOL in the short term and showed a statistical but no clinically meaningful difference in the months near death. This might be related to the fact that this intervention was not focused directly at the carer, but at the patient. Informal carers were not required to be present at each consultation and there was no systematic assessment of their wellbeing, limiting the possibility to address specific issues, such as physical wellbeing, in this group. The carers in this study were generally in bad physical health, as indicated by the SF-36v2 physical component score of 34.8 in the usual care group and 36.4 in early and systematic PC group, which is lower than the US population norm of 50. This is in line with findings that carers often place patients' needs above their own, which over time, can have negative consequences on the carers' health[31]. Interventions that are also tailored directly to the carers needs are necessary in combination with well-powered studies to better assess the effect of early and systematic integration of PC on carer's physical health.

Previous studies of early PC integrated in oncology that examined carer-reported outcomes found beneficial effects on mood or satisfaction with care but not on QOL[16,17]. In our trial, we did not find improvement in anxiety or depression nor did we find an effect of early integration of PC on satisfaction with care of carers. However, at baseline the total score of the FAMCARE in the control and the intervention group was 81 and 78 respectively which is high compared to other studies[16,32]. This might indicate that there was little room for further improvement since it is known that satisfaction questionnaires are positively skewed and might have ceiling effects[33].

Strengths of this study lie in in the prospective randomized controlled design and that for 61% (115 of 186) of patients an informal carer was included. This study has also some limitations. Firstly, it was a single-center study in a tertiary university hospital setting which limits the generalizability of the results to other care settings and clinical populations. Secondly, full blinding of the patients, carers, clinicians and assessors was not possible, which may have introduced a cross-over effect or other biases. Third, the power calculation was patient driven, carer outcomes were secondary endpoints indicating that the study might have lacked adequate statistical power to test the effect of early integration of PC on carer-reported outcomes. Fourthly, in our study the PC nurses were not required to register if the carers attended the PC consultations resulting in uncertainty of the number of PC consultations that were attended by the informal carers leading to inconclusiveness of the direct impact of the intervention.

Conclusion

Early and systematic palliative care integrated in oncology care, as opposed to palliative care on demand, improved the quality of life of informal carers of patients with advanced cancer soon after diagnosis of advanced disease and when death of the patient is approaching. This effect was found by providing a structured intervention that focused primarily on the patient and encouraged participation of carers. These findings provide additional insights into the effect of early and systematic integration of palliative care in oncology care for carers. Next to improving the quality of life of patients with advanced cancer, early palliative care interventions more directly tailored at the needs of informal carers could also improve the support to and quality of life of families.

Authors' contributions

All listed authors contributed to the writing of the article and approved the final version of the manuscript. All authors were involved in the design of the study and the figures, all authors contributed to the data interpretation and the manuscript writing. GV and KP were also responsible for the literature search. GV, SVB, EN, MD, KE, VC, and KG contributed to the data collection. Data analysis was done by GV, KP, RC and LD. All authors had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest.

We have no conflict of interest to report.

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References

1 Candy B, Jones L, Drake R, Leurent B, King M. Interventions for supporting informal caregivers of patients in the terminal phase of a disease (Review). *The Cochran* 2011.

2 Northouse L, Williams A-L, Given B, McCorkle R. Psychosocial care for family caregivers of patients with cancer. *J Clin Oncol* 2012; **30**: 1227–34.

3 Choi YS, Hwang SW, Hwang IC, *et al.* Factors associated with quality of life among family caregivers of terminally ill cancer patients. *Psychooncology* 2016; **25**: 217–24.

4 Vitaliano PP, Strachan E, Dansie E, Goldberg J, Buchwald D. Does Caregiving Cause Psychological Distress ? The Case for Familial and Genetic Vulnerabilities in Female Twins. *Ann Behav Med* 2014; : 198–207.

5 Grunfeld E, Coyle D, Whelan T, *et al.* Family caregiver burden: results of a longitudinal study of breast cancer patients and their principal caregivers. *CMAJ* 2004; **170**: 1795–801.

6 Weitzner MA, McMillan SC, Jacobsen PB. Family caregiver quality of life: Differences between curative and palliative cancer treatment settings. *J Pain Symptom Manage* 1999; **17**: 418–28.

7 Northouse L, Williams A-L, Given B, Mccorkle R. Psychosocial Care for Family Caregivers of Patients With Cancer. *J Clin Oncol* 2012; **30**: 1227–34.

8 Gaertner J, Wolf J, Ostgathe C, *et al.* Specifying WHO recommendation: moving toward disease-specific guidelines. *J Palliat Med* 2010; **13**: 1273–6.

9 Temel JS, Greer J a, Muzikansky A, *et al.* Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010; **363**: 733–42.

10 Zimmermann C, Swami N, Krzyzanowska M, *et al.* Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. *Lancet* 2014; : 1721–30.

11 Bakitas M, Lyons K, Hegel M, *et al.* The Project ENABLE II Randomized Controlled Trial to Improve Palliative Care for Patients with Advanced Cancer. *J Am Med Assoc* 2009; **302**: 741–9.

12 Bakitas MA, Tosteson TD, Li Z, *et al.* Early Versus Delayed Initiation of Concurrent Palliative Oncology Care : Patient Outcomes in the ENABLE III Randomized Controlled Trial. *J Clin Oncol* 2015; **33**: 1438–1145.

13 Maltoni M, Scarpi E, Dall M, *et al.* Systematic versus on-demand early palliative care : results from a multicentre , randomised clinical trial. *Eur J Cancer* 2016; **65**: 61–8.

14 Vanbutsele G, Pardon K, Van Belle S, *et al.* Effect of early and systematic integration of palliative care in patients with advanced cancer: A randomised controlled trial. *Lancet Oncol* 2018; **19**: 394–404.

15 Jacobs JM, Shaffer KM, Nipp RD, *et al.* Distress is Interdependent in Patients and Caregivers with Newly Diagnosed Incurable Cancers. *Ann Behav Med* 2017. DOI:10.1007/s12160-017-9875-3.

16 Mcdonald J, Swami N, Hannon B, *et al.* Impact of early palliative care on caregivers of patients with advanced cancer: cluster randomised trial. *Ann Oncol* 2017; **28**: 163–8.

17 Dionne-Odom JN, Azuero A, Lyons KD, *et al.* Benefits of Early Versus Delayed Palliative Care to Informal Family Caregivers of Patients With Advanced Cancer: Outcomes From the ENABLE III Randomized Controlled Trial. *J Clin Oncol* 2015; **33**: 1446–52.

18 El-Jawahri A, Greer JA, Pirl WF, *et al.* Effects of early integrated palliative care in patients with lung and gi cancer: A randomized clinical trial. *Oncologist* 2017; **35**: 834–41.

19 Vanbutsele G, Van Belle S, De Laat M, *et al.* The systematic early integration of palliative care into multidisciplinary oncology care in the hospital setting (IPAC), a randomized controlled trial: The study protocol. *BMC Health Serv Res* 2015; **15**. DOI:10.1186/s12913-015-1207-3.

20 Ware JE, Kosinski M, Gandek B, *et al.* The Factor Structure of the SF-36 Health Survey in 10 Countries. *J Clin Epidemiol* 1998; **51**: 1159–65.

21 Farivar SS, Cunningham WE, Hays RD. Correlated physical and mental health summary scores for the SF-36 and SF-12 Health Survey, V.1. *Health Qual Life Outcomes* 2007; **5**. DOI:10.1186/1477-7525-5-54.

22 Hann M, Reeves D. The SF-36 scales are not accurately summarised by independent physical and mental component scores. *Qual Life Res* 2008; **17**: 413–23.

23 Samsa G, Edelman D, Rothman ML, Williams GR, Lipscomb J, Matchar D. Determining clinically important differences in health status measures: A general approach with illustration to the Health Utilities Index Mark II. *Pharmacoeconomics* 1999; **15**: 141–55.

24 Kristjanson LJ. Validity and reliability testing of the famcare scale: Measuring family satisfaction with advanced cancer care. *Soc Sci Med* 1993; **36**: 693–701.

25 Harding R, Higginson IJ. What is the best way to help caregivers in cancer and palliative care? A systematic literature review of interventions and their effectiveness. *Palliat Med* 2003; **17**: 63–74.

26 Li Z, Frost HR, Tosteson TD, *et al.* A semiparametric joint model for terminal trend of quality of life and survival in palliative care research. *Stat Med* 2017; **36**: 4692–704.

27 Northouse LL, Mood DW, Schafenacker A, *et al.* Randomized clinical trial of a family intervention for prostate cancer patients and their spouses. *Cancer* 2007; **110**: 2809–18.

28 Otis-Green S, Juarez G. Enhancing the Social Well-Being of Family Caregivers. *Semin Oncol* 20012; **28**: 246–55.

29 Wadhwa D, Burman D, Swami N, Rodin G, Lo C, Zimmermann C. Quality of life and mental health in caregivers of outpatients with advanced cancer. *Psychooncology* 2013; **22**: 403–10.

30 McDonald J, Swami N, Pope A, *et al.* Caregiver quality of life in advanced cancer: Qualitative results from a trial of early palliative care. *Palliat Med* 2018; **32**: 69–78.

31 Northouse LL, Katapodi MC, Song L, Zhang L, Mood DW. Interventions with family caregivers of cancer patients: meta-analysis of randomized trials. *CA Cancer J Clin* 2010; **60**: 317–39.

32 Hannon B, Swami N, Krzyzanowska MK, *et al.* Satisfaction with oncology care among patients with advanced cancer and their caregivers. *Qual Life Res* 2013; **22**: 2341–9.

33 Carter GL, Lewin TJ, Gianacas L, Clover K, Adams C. Caregiver satisfaction with out-patient oncology services: Utility of the FAMCARE instrument and development of the FAMCARE-6. *Support Care Cancer* 2011; **19**: 565–72.

Chapter 7:

The effect of early and systematic integration of palliative care in oncology on quality of life and health care use near the end-of-life: a randomized controlled trial.

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Submitted

Abstract

Background: This study evaluated the effect of early integrated palliative care (PC) in oncology on quality of life (QOL) near the end of life and use of health care resources near the end-of-life.

Methods: Patients with advanced cancer and a life expectancy of approximately one year were randomly assigned to either early and systematic integration of PC into oncological care (intervention) or standard oncological care alone (control). QOL was assessed with the EORTC QLQ-C30 global health status/QOL scale and McGill Quality of Life (MQOL) Single Item Scale and Summary Scale at baseline, 12 weeks and six weekly thereafter until death. Use of health care resources was collected from chart review in patient's electronic medical file.

Results: Of the 186 randomized patients, 147 participants of the original sample had died by November 2017. When applying the terminal decline model, patients in the intervention group scored significantly higher on global health status/quality of life of the EORTC QLQ C30, at six months (difference: 5.9 [0.06; 11.1], p=0.03), three (difference: 6.8 [1.0; 12.6], p=0.02) and one month (difference: 7.6 [0.7; 14.5], p=0.03) prior to the patient's death compared to the control group. Similar results were found for the Single Item Scale and Summary Score of the MQOL. We did not observe differences in use of health care resources between groups.

Discussion: Early integrated palliative care in oncology is a valuable approach since it also increase QOL near the end-of life and not only soon after initiation of PC.

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Introduction

Treatment goals for people with progressive life-shortening diseases ideally move from curative or life prolonging therapies to comfort care as they approach the end of life. However, care for people with cancer has been criticized for frequently being overly aggressive near the end-of-life[1]. Research - shows that substantial proportions of cancer patients receive chemotherapy in the last seven days of life, have multiple hospitalizations or emergency department (ED) visits in the last thirty days of life, or die in acute care facilities[2–4]. These are in most cases considered to be indicators of poor-quality care[5,6]. Research has also shown that stays in the intensive care unit in the last weeks of life and dying in the hospital are important determinants of poor quality of life (QOL) at the end of life (EOL) of cancer patients. Important predictors of better QOL at the EOL, on the other hand, include measures of patients feelings treated as a whole person by the team and feeling comfortable asking questions about their care[7].

Early integration of palliative care (PC) in oncology care has been developed to provide guidance about symptom management and discussions on goals of care that engage patients and families to consider their values and care preference of end-of-life care and to improve quality of life of patients with advanced disease. This new care approach, as opposed to PC which is traditionally only applied in later stages of the disease trajectory, has been examined in several studies and consistently showed beneficial effects on patient-reported outcomes such as quality of life and mood at 3 or 4 months after diagnosis for patients with advanced cancer[8–12]. The quality of care at the end-of-life, however, represents another important outcome of palliative care. Most studies of early integration of palliative care in oncology also examined the effect on use of health care resources and aggressiveness of care at the end-of-life. Three[10,11,13] studies found some differences in use of health care resources indicating better end-of-life care: such as less chemotherapy in last days before death or more hospice admissions in favor of the early palliative care arm. Other studies did not find any difference in healthcare utilization at the end-of-life between early palliative care and usual care[8,14].

Despite the link in research between quality of end-of-life care and QOL at the EOL, evidence of early integration of palliative care on QOL at the EOL is less extensive and only originates from the United States. Three studies[8,9,14] have examined QOL near death of patients with advanced cancer and two studies[8,9] found benefits in QOL in favor of early integration of palliative care.

We conducted a randomized controlled trial of early and systematic integration of palliative care in oncology care in the Belgian health care setting. In a previous paper, we focused on the primary outcome and revealed benefits in QOL soon after diagnosis or prognosis in favor of early and systematic palliative care[15]. In a present secondary analysis, the aim is to examine whether early integrated

palliative care in oncology care influenced QOL at the EOL and the use of health care resources near the end-of-life of patients with advanced cancer.

Methods

Study Patients

Patients treated at the Medical Oncology department, Thoracic Oncology department and Digestive Oncology department of the Ghent University Hospital (Flanders, Belgium) were eligible to be enrolled if they were 18 years or older, had an advanced cancer diagnosis (histologically or cytologically confirmed) due to a solid tumour, a European Cooperative Oncology Group performance status of 0–2, an estimated life expectancy of 12 months (assessed by the treating oncologist), were within the first 12 weeks of a diagnosis of a new primary tumour or had a recent diagnosis of progression, and were able to read and respond to questions in Dutch. Patients recruited from a hospital other than Ghent University Hospital had to be within the first 12 weeks of disease progression or still on first-line treatment. Out – as well as inpatients were considered for inclusion[15].

Study procedures

From April 29, 2013 to February 29, 2016, we randomly assigned participants with advanced cancer in a one to one fashion (with stratification for department) to receive either early and systematic palliative care integrated in usual care or usual care alone. Participants who were assigned to the intervention arm consulted with nurses from the PC team within three weeks of enrollment and monthly thereafter. Additional palliative care consultations could be scheduled at the discretion of the patients. The intervention consisted of four major components: (1) training sessions on the medical aspects of the different cancer diagnoses by oncologists for the PC team (2) semi structured monthly palliative care consultations that focused on illness understanding, symptom burden, support in decision making, and support for emotional, social and/or spiritual needs, (3) monthly symptom assessments using Edmonton Symptom Assessment Scale and (4) integration of PC into oncological care through participating in the weekly multidisciplinary oncology meetings and reporting in the electronic patient files. A detailed description of the intervention is reported elsewhere[16]. Patients assigned to usual care only met with the PC team on demand of the patient or treating physician, these patients did not cross-over to the early and systematic PC arm. The Ethical Committee of the Ghent University Hospital approved the study protocol before initiation; oncologists introduced the study to patients and all participants provided written informed consent.

Data collection and study outcomes

Questionnaires measuring socio-demographic information and quality of life were administered at baseline, QOL was further assessed at 12 weeks and six-weekly thereafter until death of the patient. Quality of life was measured with the global health status/quality of life scale of the EORTC QLQ-C30, a two-item scale that is converted to a 0-100 scale[17]. It was also measured with Single Item Scale and Summary Score of the McGill Quality of Life Questionnaire (MQOL) that weighs the domains (physical, psychological, existential/spiritual, and social) of quality of life equally[18]. For this analysis, we looked at the quality-of-life measures at six, three and one month prior to death.

For participants who had died by November 8th 2017 while participating in the trial, the electronic medical records were reviewed to obtain data such as type of treatment at baseline, dates of hospitalization, dates of discharge, location of hospitalization, date of last treatment, time of death and place of death at the Ghent University Hospital. The indicators of use of health care resources at the end-of-life are based on the literature [3,10,19,20]. These include (1) any emergency room (ER) visit, any intensive care unit (ICU) admission, any hospital admission, more than 2 hospital admissions, hospitalizations longer than 14 days, or systemic treatment in the last 30 days of life (2) admission in the palliative care unit and (3) hospital death. We also used a composite aggressive end-of-life care score[21] in which 1 point is given for each of the 6 indicators that occurred in the last 30 days of life : death in the hospital, 2 ER visits, 2 hospital admissions, >14 days of hospitalization, an ICU admission, or receipt of chemotherapy. A higher score is indicative of more aggressive care.

Statistical analysis

The patient's quality of life at 12 weeks was the primary outcome on which this study was powered, resulting in a sample size of 186 patients with advanced cancer. We performed statistical analysis using SPSS software (version 25), SAS (version 9.4) and R (version 3.4.1). Data obtained from April 29 2013 to November 8 2017 were included. All patients were analyzed according to their original randomization. A terminal decline joint model[22] was applied to model patient's QOL backward from the time of death rather than prospectively from the time of enrolment[22] for all patients with a baseline measure . This approach controls for the known relationship between the deterioration in QOL as the patient's death is nearing. It combines two sub-models to analyze both the terminal trend of the outcome scores of QOL (EORTC QLQ C30 global health/quality of life scale; the Single Item Scale and the Summary Score of the MQOL) and survival. This is a recent technique that has the advantage of considering the dependence between QOL and survival while accounting for missing data and is often used in early palliative care trials[9,23]. The first sub-model is a semi-parametric mixed effects model to compare the longitudinal trend of the outcome scores between groups, including variables 'department' (the stratification factor) and 'baseline scores' as covariates. The second sub-model is a Cox model comparing the survival

outcomes between groups correcting for department. The knots were selected based on Akaike information criterion (AIC). All analyses were applied using R code made available by the authors Li et al[22]. For each time point of interest (six, three and one month prior to death), a model-based 95% confidence interval for the mean outcome score is presented. For the indicators of use of health care services, logistic regression was applied, adjusting for the stratification factor. In case of complete separation, exact logistic was applied in SAS version 9.4 with group and department as predictors. The observed proportions are reported in combination with Wilson score 95% confidence intervals. This trial is registered with ClinicalTrials.gov, number NCT01865396.

Results

Patient Characteristics

Of the 358 eligible patients presenting to the Medical Oncology, Thoracic Oncology and Digestive Oncology department from April 29, 2013, through Feb 29, 2016, 186 were enrolled into the study (Figure 1). Baseline characteristics are shown in Table 1. Sixty-nine percent of the patients were male, 48% was between 55 and 64 years old, the most frequent cancer diagnosis was advanced gastrointestinal (38%) or digestive cancer (28%). By November 8th 2017, 147 participants of the original sample had died. Baseline characteristics of patients that died while participating in the trial are shown in Supplementary Table 1.

Figure 1: Trial profile

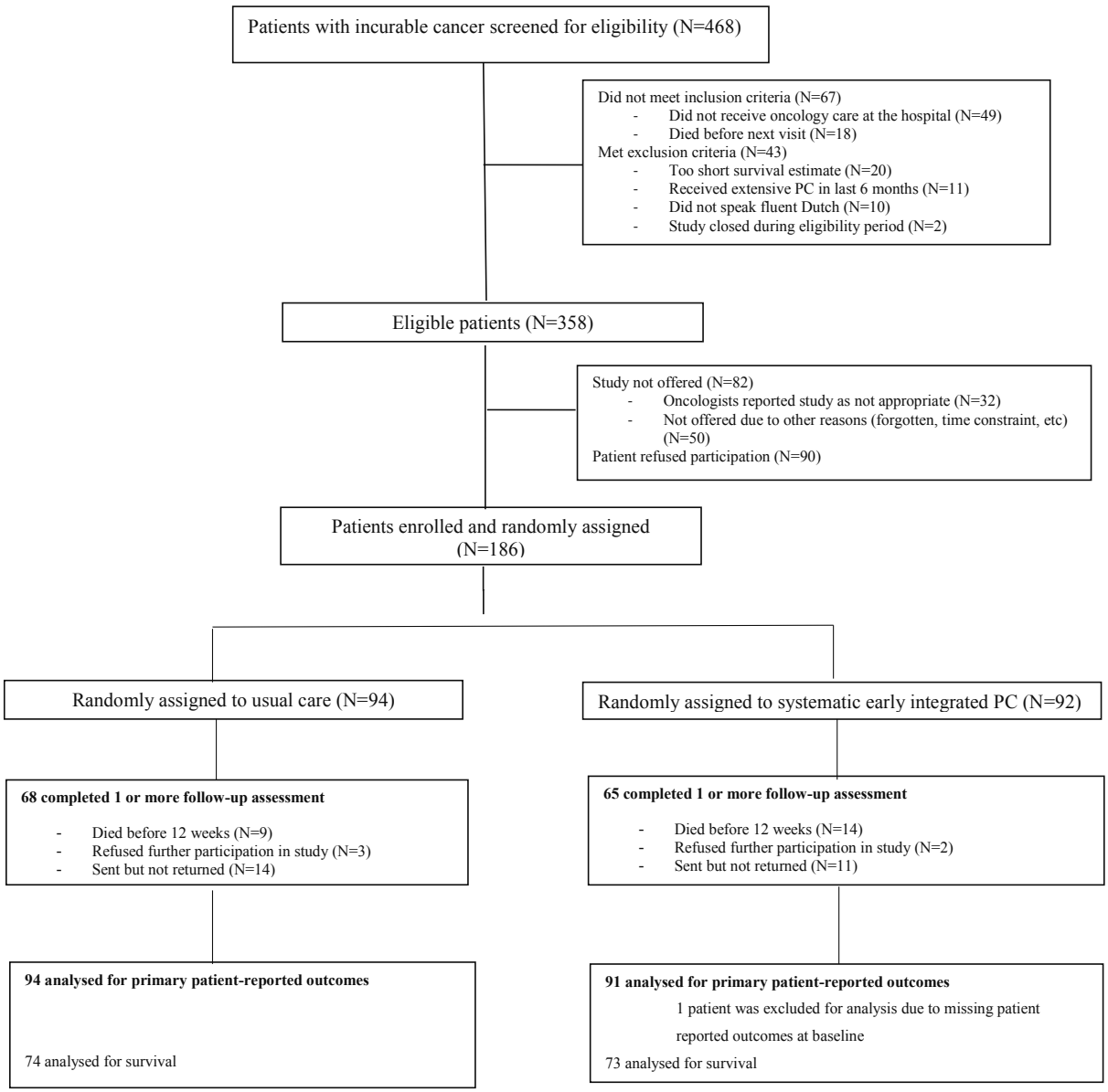


Table 1: Baseline characteristics

	Usual Care (N=94)	Early Integrated Care (N=91)
Gender n° (%)		
Male	69 (73)	58 (64)
Female	25 (27)	33 (36)
Age		
18 –54 year old	18 (19)	19 (21)
55- 64 year old	46 (49)	43 (47)
65 -85 year old	30 (32)	29 (32)
Education no (%)*		
Less than high school	2 (2)	3 (3)
Less than higher level in high school	62 (66)	52 (59)
College or university	30 (32)	33 (38)
ECOG Performance Status no(%)|		
0 - the patient is asymptomatic	22 (23)	35 (39)
1 - the patient is symptomatic but fully ambulatory	53 (56)	46 (51)
2 - the patient is symptomatic and in bed less than 50% of the day	13 (14)	8 (9)
3 - Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	6 (6)	2 (2)
Tumour Site		
Gastrointestinal	36 (38)	35 (39)
Lung	26 (28)	25 (28)
Head&Neck	12 (13)	7 (8)
Breast	7 (7)	7 (8)
Melanoma	7 (7)	8 (9)
Genitourinary	6 (6)	9 (10)
Department		
Medical Oncology	36 (38)	35 (39)
Digestive Oncology	32 (34)	31 (34)
Thoracic Oncology	26 (28)	25 (28)

ECOG- Eastern Cooperative Oncology group

*Three values missing for early and systematic palliative care group.

| At screening, all patients with ECOG performance status of less than two were selected, eight patients deteriorated to ECOG performance status of 3 at baseline, these patients were not excluded.

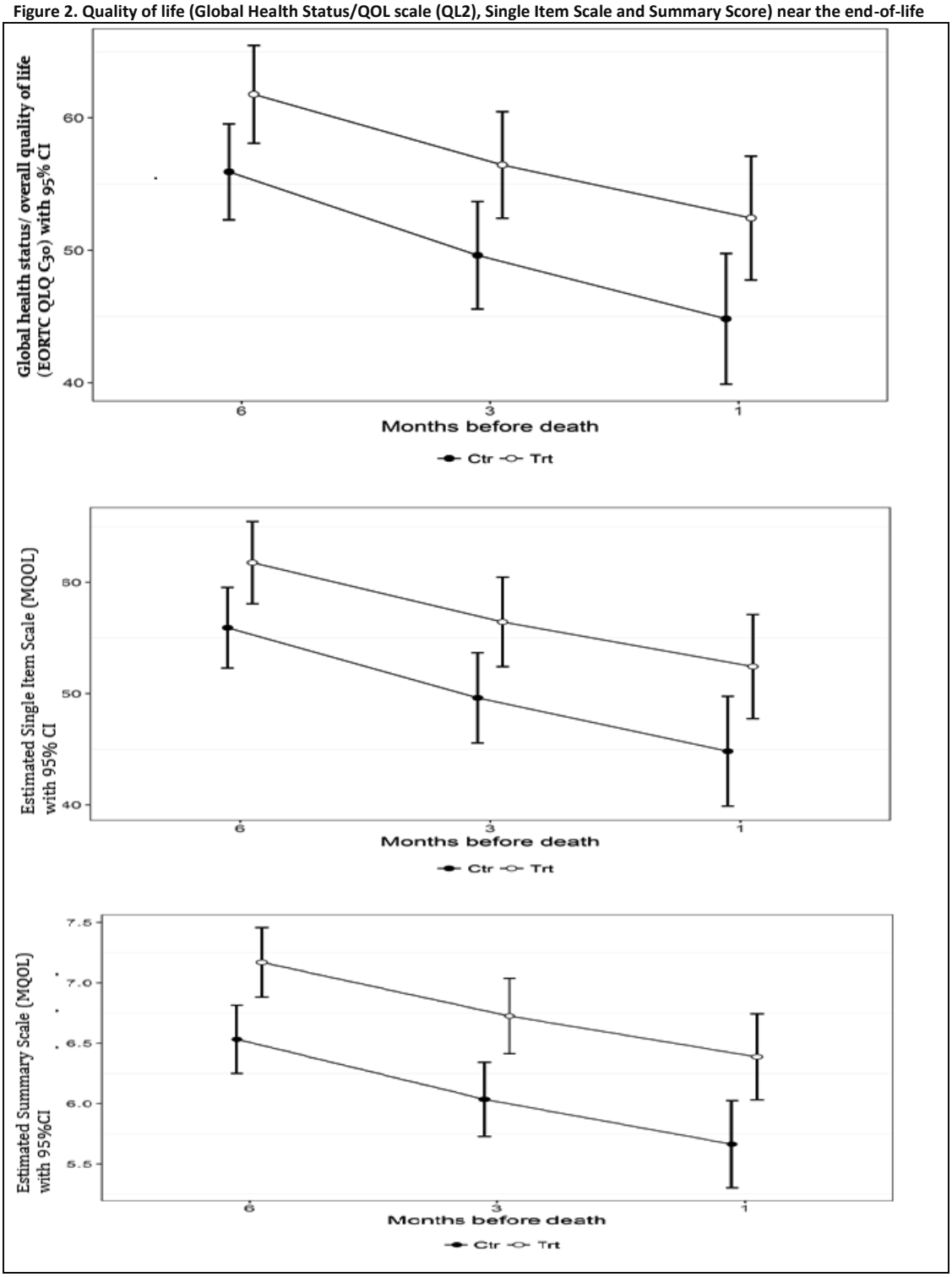
Palliative care visits

Eighty-five patients (92%) in the intervention arm attended at least one palliative care consultation (median 6; interquartile range (IQR) 2- 11.5), 41 control patients (44%) received at least one palliative care consultation (median 0; IQR 0-2) within the trial period.

Quality of life near the end-of-life

When applying the terminal decline model, patients in the intervention group scored significantly higher on global health status/quality of life of the EORTC QLQ C30, at six months (difference: 5.9 [0.06; 11.1], p=0.03), three (difference: 6.8 [1.0; 12.6], p=0.02) and one month (difference: 7.6 [0.7; 14.5], p=0.03) prior to the patient's death compared to the control group. Significantly higher scores for patients in the intervention group were also found in the Single Item Scale (difference: 6 months: 1.2 [0.6-1.8],p= < 0.0001; 3 months: 1.6 [0.8-2.1], p= < 0.0001; 1 month: 0.6 [-0.3-1.4], p= < 0.0001) and Summary Score of the MQOL (difference: 6 months: 0.6 [0.2-1.1],p= 0.002; 3 months: 0.7 [0.3-1.1], p= 0.002; 1 month: 0.7 [0.2-1.2], p= 0.005). (See Figure 2).

Figure 2. Quality of life (Global Health Status/QOL scale (QL2), Single Item Scale and Summary Score) near the end-of-life



Use of health care resources

When examining the use of health care resources in the last 30 days of life, we observed no significant different odds between the intervention group and the control group (See Table 2). The estimated percentages of patients being hospitalized in the last 30 days of life in the intervention group (61% [47-74]) did not differ significantly from the control group (42% [30-56], p= 0.06), nor did receiving systematic treatment in the last 30 days differ (intervention: 35% [24-48]; control: 29% [18-41], p= 0.45). We did not observe significant difference odds for patients that died on a hospital ward in the Ghent University Hospital (intervention: 45% [32-59]; control: 30% [19-44], p= 0.16) or at the palliative care unit (intervention: 14% [8-25]; control 11% [5-22], p= 0.6). . The odds for aggressive end-of-life care were also not significantly different between both groups (p= 0.42).

Table 2. Indicators of use of health care resources at the end-of-life

	Estimated percentages [95CI]		Early integrated care (vs. Usual Care) OR [95CI]	p-value
	Usual Care (n=63)	Early Integrated Care (n=65)		
Within last 30 d of life				
Any ER visit*				0.12
Yes (vs No)	0 [0-7]	4 [1-14]	3.0 [0.4- +inf]	
Any hospital admission				0.06
Yes (vs No)	42 [30 - 56]	61 [47-74]	2.2 [1.0 -4.7]	
≥ 2 hospital admissions*				0.33
Yes (vs No)	9 [4-19]	18 [10-30]	2.1 [0.6-8.8]	
>14 d of hospitalization				0.80
Yes (vs No)	19 [10 -32]	17 [9-30]	0.9 [0.3-2.4]	
Hospital death§				0.16
Yes (vs No)	30 [19-44]	45[32-59]	1.8 [0.7-4.8]	
ICU admission*				0.41
Yes (vs No)	2 [0-9]	0 [0-6]	0.7 [0.0- 13.4]	
Systemic treatment				0.45
Yes (vs No)	29 [18-41]	35 [24-48]	1.3 [0.6-2.9]	
Palliative Care Unit admission				0.60
Yes (vs No)	11 [5-22]	14 [8-25]	1.3 [0.5-3.8]	
Aggressive EOL care score||				0.42
0 (vs ≥ 3)	57 [46-69]	46 [35-59]	0.79 [0.3-2.4]	
1 (vs ≥ 3)	27 [17-39]	29 [18-40]	1.0 [0.3-3.4]	
2 (vs ≥ 3)	8 [2-25]	17 [8-26]	2.0 [0.5-8.1]	

ICU; Intensive Care Unit ER: Emergency room EOL: End-of-life care
*Exact logistic regression was applied
§ Hospital death at the Ghent University, except death at palliative care unit.
|| For the composite score of aggressiveness of end-of-life care the reference category of three indicators or more was chosen because only 4 participants had a score of 4 and none had a score of 5 or 6.

Discussion

This study shows that early and systematic integration of palliative care concurrent with oncology care results in higher quality of life at six, three and one month prior to death of patients with advanced cancer. The intervention had no apparent effect on the use of health care resources or aggressiveness of care at the end-of-life.

To our knowledge, this is the first European study that examined the effect of early integration of palliative care in oncology on quality of life (QOL) near the end-of-life of cancer patients. Further strengths of this study lies in the prospective randomized controlled design. This study has also some limitations. First, we did not prespecify the terminal decline joint modelling approach in our protocol as we were unaware of that approach at that time. As a result, we did not plan the sample size to evaluate quality-of-life near death. Secondly, we are not able to exclude a cross-over effect since full blinding of the patients, clinicians and assessors was not possible. Third, data of use health care services is based on data collection via chart review of the University Hospital, it is possible that we may have missed use of resources of participants who transferred their care. The use of routinely collected comprehensive databases could address this limitation[24]. Fourthly, attainment of one goals of care is also an important outcome of end-of-life care. We did not assess patient's preferences of end-of-life care and hence, are not able to evaluate the extent of concordance between preferences and the care received[25].

The research field of early palliative care in cancer is relatively new and has mostly focused on the effect of quality of life earlier in the disease trajectory. In this study, we explored the effect of early integration of palliative care in oncology on quality of life near the end-of-life. We found statistically significant beneficial effects in QOL at the EOL by providing patients with monthly semi-structured consultations with a specialized palliative care nurse, starting early in the disease trajectory and continuing until death. The plausible mechanism of the long term benefit of early integrated palliative care, versus on-demand palliative care, could be related to the fact that patients and palliative care professionals have more time to build a relationship, to focus on coping with the progressive and worsening illness, to address decision making in relation to cancer treatment and end-of-life care and to enhance symptom assessment and management. Research has shown that adequate symptom management, effective communication and a strong therapeutic bond contribute to quality end-of-life care[26–28].

Our results are consistent with the literature since we observe lower quality of life when death approaches in both groups[8,9]. However, our result also suggest an increasing difference in quality of life between the two groups over time, with a growing benefit for patients receiving early integrated palliative care with the largest discrepancy at one month prior to death. The EORTC QLQ C30 has cited a difference of 7.5 to be clinically meaningful[29] and we found such a difference between the two patient groups at one month prior to death. Therefore, we can conclude that differences in quality of life at one

month achieved clinical significance in addition to statistical significance in favor of early and integrated PC. These results in combination with the positive effects on quality of life early in the disease trajectory highlight the importance of early integration of palliative care in. oncology[30].

It was hypothesized that early integrated palliative care would enhance decision-making in relation to cancer treatment and would reduce the use of health care resources at the end-of-life such as hospitalizations or systemic treatment in the last days of life. Our results, however, did not demonstrate a differences and are inconsistent with the findings of three previous trials of early palliative care [10,13]. The latter were based upon a physician-led intervention as opposed to this primarily nurse-led intervention. Other trials of early integrated palliative care with primarily nurse-led interventions also did not find significant differences in reduced use of hospital, ICU or ED resources compared to usual care[8,14]. This might indicate that nurse-led interventions are less effective in reducing the use of health care resources indicative of poor quality of care for patients with advanced cancer.

On the other hand, we observed that 77% of all deceased participants scored one or less on the composite score of aggressive end-of-life care. Overall, this indicates low levels of aggressiveness of end-of-life care compared to other studies where 86% of cancer decedents had at least one indicator of aggressive care or more [21]. This could imply that there was little opportunity for the intervention to decrease the aggressiveness of end-of-life.

Last, the benefits of early palliative care on end-of-life QOL in combination with absence of effect on indicators of poor end-of-life care could also indicate that the level of integration of our intervention was too limited to observe differences in health care resources. An influential article has proposed three levels of integration: linkage, coordination and full integration[31,32]. At the highest level of integration, multidisciplinary teams manage all care and provide care and transitions in care in all key settings. In our intervention, we were not able to reach this level of clinical integration, the focus of the intervention was more on providing a patient-centered care approach[32], with mechanisms of referral and follow-up to the oncology team. It is plausible that the lack of full integration of early palliative care may have limited the impact on health care utilization on indicators of poor quality of end-of-life care.

Conclusion

Early integrated palliative care in oncology, as opposed to palliative care on demand, results in improved end-of-life quality of life. This effect was found by providing semi-structured consultations with primarily specialized palliative care nurses. Not only was QOL better throughout the disease trajectory, the difference in benefit also increased towards the end-of-life. No differences in health care utilization at the end-of-life or aggressiveness of end-of-life care were found. More research is needed with regards

to the components of early integrated palliative care that could lead to less use of health care resources that are indicators of poor quality of end-of-life care.

Authors' contributions

All listed authors contributed to the writing of the article and approved the final version of the manuscript. All authors were involved in the design of the study and the figures, all authors contributed to the data interpretation and the manuscript writing. GV and KP were also responsible for the literature search. GV, SVB, EN, MD, KE, VC, and KG contributed to the data collection. Data analysis was done by GV, KP, RC and LD. All authors had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest

We have no conflict of interest to report.

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References

1 De Schreye R, Smets T, Annemans L, *et al.* Applying quality indicators for administrative databases to evaluate end-of-life care for cancer patients in Belgium. *Health Aff* 2017; **36**: 1234–43.

2 Earle CC, Neville BA, Landrum MB, *et al.* Evaluating claims-based indicators of the intensity of end-of-life cancer care. *Int J Qual Heal Care* 2005; **17**: 505–9.

3 Earle CC, Landrum MB, Souza JM, Neville BA, Weeks JC, Ayanian JZ. Aggressiveness of cancer care near the end of life: Is it a quality-of-care issue? J. Clin. Oncol. 2008; **26**: 3860–6.

4 Lamont EB, Christakis NA. Physician factors in the timing of cancer patient referral to hospice palliative care. *Cancer* 2002; **94**: 2733–7.

5 Hui D, Kim SH, Roquemore J, Dev R, Chisholm G, Bruera E. Impact of timing and setting of palliative care referral on quality of end-of-life care in cancer patients. *Cancer* 2014; **120**: 1743–9.

6 Earle CC, Landrum MB, Souza JM, Neville BA, Weeks JC, Ayanian JZ. Aggressiveness of cancer care near the end of life: Is it a quality-of-care issue? J. Clin. Oncol. 2008; **26**: 3860–6.

7 Zhang B, Nilsson ME, Prigerson HG. Factors important to patients' quality of life at the end of life. *Arch Intern Med* 2012; **172**: 1133–42.

8 Bakitas M, Lyons K, Hegel M, *et al.* The Project ENABLE II Randomized Controlled Trial to Improve Palliative Care for Patients with Advanced Cancer. *J Am Med Assoc* 2009; **302**: 741–9.

9 Temel JS, Greer JA, El-jawahri A, *et al.* Effects of Early Integrated Palliative Care in Patients With Lung and GI Cancer : A Randomized Clinical Trial. *J Clin Oncol* 2017; : 1–17.

10 Temel JS, Greer J a, Muzikansky A, *et al.* Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010; **363**: 733–42.

11 Zimmermann C, Swami N, Krzyzanowska M, *et al.* Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. *Lancet* 2014; : 1721–30.

12 Maltoni M, Scarpi E, Dall M, *et al.* Systematic versus on-demand early palliative care : results from a multicentre , randomised clinical trial. *Eur J Cancer* 2016; **65**: 61–8.

13 Maltoni M, Scarpi E, Dall'Agata M, *et al.* Systematic versus on-demand early palliative care: A randomised clinical trial assessing quality of care and treatment aggressiveness near the end of life. *Eur J Cancer* 2016; **69**: 110–8.

14 Bakitas MA, Tosteson TD, Li Z, *et al.* Early Versus Delayed Initiation of Concurrent Palliative Oncology Care : Patient Outcomes in the ENABLE III Randomized Controlled Trial. *J Clin Oncol* 2015; **33**: 1438–1145.

15 Vanbutsele G, Pardon K, Van Belle S, *et al.* Effect of early and systematic integration of palliative care in patients with advanced cancer: A randomised controlled trial. *Lancet Oncol* 2018; **19**: 394–404.

16 Vanbutsele G, Van Belle S, De Laat M, *et al.* The systematic early integration of palliative care into multidisciplinary oncology care in the hospital setting (IPAC), a randomized controlled trial: The study protocol. *BMC Health Serv Res* 2015; **15**. DOI:10.1186/s12913-015-1207-3.

17 Fayers P, Bottomley A. Quality of life research within the EORTC—the EORTC QLQ-C30. *Eur J Cancer* 2002; **38**: 125–33.

18 Cohen SR, Mount BM, Bruera E, Provost M, Rowe J, Tong K. Validity of the McGill Quality of Life Questionnaire in the palliative care setting: a multi-centre Canadian study demonstrating the importance of the existential domain. *Palliat Med* 1997; **11**: 3–20.

19 Ho TH, Barbera L, Saskin R, Lu H, Neville BA, Earle CC. Trends in the aggressiveness of end-of-life cancer care in the universal health care system of Ontario, Canada. *J Clin Oncol* 2011; **29**: 1587–91.

20 Hui D, Didwaniya N, Vidal M, *et al.* Quality of end-of-life care in patients with hematologic malignancies: A retrospective cohort study. *Cancer* 2014; **120**: 1572–8.

21 Tang ST, Wu SC, Hung YN, Chen JS, Huang EW, Liu TW. Determinants of aggressive end-of-life care for Taiwanese cancer decedents, 2001 to 2006. *J Clin Oncol* 2009; **27**: 4613–8.

22 Li Z, Frost HR, Tosteson TD, *et al.* A semiparametric joint model for terminal trend of quality of life and survival in palliative care research. *Stat Med* 2017; **36**: 4692–704.

23 Bakitas M, Sc DN, Lyons KD, *et al.* The project ENABLE II randomized controlled trial to improve palliative care for rural patients with advanced cancer : Baseline findings , methodological challenges , and solutions. *Palliat Support Care* 2009; **7**: 75–86.

24 Maetens A, De Schreye R, Faes K, *et al.* Using linked administrative and disease-specific databases to study end-of-life care on a population level. *BMC Palliat Care* 2016; **15**: 1–10.

25 Mack JW, Weeks JC, Wright AA, Block SD, Prigerson HG. End-of-life discussions, goal attainment, and distress at the end of life: Predictors and outcomes of receipt of care consistent with preferences. *J Clin Oncol* 2010; **28**: 1203–8.

26 Zhang B, Nilsson M, Prigerson HG. Factors important to patients' quality of life at the end of life.; - Archives of internal medicine. - *Arch Intern Med* 2012; **172**: 1133–42.

27 Quill TE. Initiating end-of-life discussions with seriously ill patients: Addressing the 'elephant in the room'. *J Am Med Assoc* 2000; **284**: 2502–7.

28 Mack JW, Block SD, Nilsson M, *et al.* Measuring therapeutic alliance between oncologists and patients with advanced cancer: The human connection scale. *Cancer* 2009; **115**: 3302–11.

29 King MT. The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30. *Qual Life Res* 1996; **5**: 555–67.

30 Beernaert K, Deliens L, Pardon K, *et al.* What Are Physicians' Reasons for Not Referring People with Life-Limiting Illnesses to Specialist Palliative Care Services? A Nationwide Survey. *PLoS One* 2015.

31 Leutz W.N. Five Laws For Integrating Medical and Social Services: Lessons from the United States and the United Kingdom. *Milbank Q* 1999; **77**: 77–110.

32 Kaasa S, Loge JH. Early integration of palliative care—new evidence and old questions. *Lancet Oncol* 2018; **19**: 280–1.

Supplementary Table 1: Baseline characteristics of deceased participants.

	Usual Care (N=74)	Early Integrated Care (N=73)
Gender n° (%)		
Male	54 (73)	44 (60)
Female	20 (27)	29 (40)
Age		
18 –54 year old	14 (19)	14 (19)
55- 64 year old	36 (49)	34 (47)
65 -85 year old	24 (32)	25 (34)
Education no (%)*		
Less than high school	2 (3)	2 (3)
Less than higher level in high school	49 (66)	44 (62)
College or university	23 (31)	25 (35)
ECOG Performance Status no(%)|		
0 - the patient is asymptomatic	16 (22)	24 (33)
1 - the patient is symptomatic but fully ambulatory	42 (57)	40 (55)
2 - the patient is symptomatic and in bed less than 50% of the day	12 (16)	7 (10)
3 - Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	4 (5)	2 (3)
Tumour Site		
Gastrointestinal	32 (43)	32 (44)
Lung	19 (26)	19 (26)
Head&Neck	9 (12)	3 (4)
Breast	6 (8)	7 (10)
Melanoma	4 (5)	6 (8)
Genitourinary	4 (5)	6 (8)
Department		
Medical Oncology	23 (31)	22 (30)
Digestive Oncology	32 (43)	32 (44)
Thoracic Oncology	19 (26)	19 (26)

ECOG- Eastern Cooperative Oncology group

*Two values missing for early and systematic palliative care group.

| At screening, all patients with ECOG performance status of less than two were selected, six patients deteriorated to ECOG performance status of 3 at baseline, these patients were not excluded.

Part V

General discussion and conclusions

Chapter 8:

General discussion and conclusions

8.1 Introduction

In the introductory chapter of this dissertation, we formulated our research questions about challenges of palliative care in oncology and the effects of early integration of palliative care in oncology. In this section, the main findings are briefly summarized and discusses, we address the strengths and limitations of the studies mentioned in this dissertation. Finally, a number of recommendations for future research, policy and practice will be outlined.

8.2 Summary of the main findings

In **chapter 2** we discussed the prevalence and variability over time of symptoms of major depression (MD) and associated factors in a population of cancer patients enrolled in a palliative care program. The results showed a high prevalence of symptoms of MD with a strong decrease over time but also revealed significant variation in the individual trajectories. Higher anxiety, higher pain, lower performance status and lower levels of physical functioning increased to chances of reporting symptoms of MD. We underlined the importance of frequently screening for symptoms of major depression in patients with advanced cancer.

The differences between cancer types in the use and timing of referral to specialized palliative care services and reasons for non-referral were examined in **chapter 3** based upon a mortality follow-back study. When looking at differences in cancer types, hematologic cancer patients had lower chances of using palliative care services (SPCS) compared to patients with solid cancers. The use of SPCS in Belgium for cancer patients varied from 56% for hematologic cancer to 86% for head and neck cancer. We also found evidence of late referral for all cancer types, ranging from 29 days (breast) to 10 days (hematologic) prior to death. Patients with hematologic cancers also most often received treatment aimed at life prolongation or curation in the last week of life. When examining the most prevalent reason for non-referral, physicians most often reported that regular care sufficiently addressed palliative and supportive care needs and that referral to SPCS was not meaningful or not meaningful enough.

In **Chapter 4** we highlighted that studies of early integration of palliative care in oncology originated from the United States and Canada and that there was a need for similar research in Europe. We described the protocol of the randomized controlled trial we set out to conduct in Belgium to evaluate the effect of early and systematic integration of palliative care in standard oncology care. We planned to recruit 182 patients with advanced cancer from the departments of Medical Oncology, Digestive Oncology and Thoracic Oncology of the Ghent University Hospital. We further explained that patients and informal carers would be asked to fill out questionnaires on quality of life (QOL), mood, illness understanding and satisfaction with

care and that outcome measures of survival and end-of-life care would be collected from electronic patient files.

The aim of **chapter 5** was to examine whether early and systematic integration of palliative care alongside standard psychosocial oncological care provides added benefit compared with usual care for advanced cancer patients with an estimated life expectancy of 12 months. Patients who were allocated to early and systematic integration of palliative care showed an increase in overall QOL at 12 (primary outcome) and 18 weeks after baseline compared to patients in usual care. Early integration of palliative care did not lead to significant differences in survival. Inconclusive results were found on symptoms and functioning and we did not find any differences in mood or illness understanding.

Chapter 6 described the effect of early and systematic integration of palliative care in oncology on self-reported outcomes of informal carers of patients with advanced cancer. Informal carers of patients in the intervention group reported greater improvements in the mental component score (MCS) of QOL at 18 weeks. QOL (PCS and MCS) of carers in the intervention group was also significantly higher one, three and six months prior to death. No improvements were found in the physical component score (PCS) of QOL, mood, satisfaction with care or illness understanding at 12 or 18 weeks.

The aim of the study in **chapter 7** was to describe the effect of early and systematic integration of palliative care in oncology on patient-reported QOL near the end-of-life and on the use of health care resources near the end-of-life. Patients receiving early and systematic integration of palliative care reported higher quality of life at six, three and one month prior to death. We did not observe any difference in the use of health care resources near the end-of-life between both groups.

8.3. Methodological considerations, strength and limitations

To be able to answer our research questions, we performed three studies. The methodological strengths and limitations are discussed below.

8.3.1. Study 1: An international prospective cohort study among cancer patients enrolled in a palliative care program.

We estimated the prevalence and variability over time of symptoms of major depression in patients with cancer enrolled in a palliative care program (Chapter 2). We used data from the European Palliative Care Cancer Symptom (EPCCS) study, an international prospective cohort study[1]. This study has several strengths. First, this study is based on a large sample of patients (n=1739) with incurable cancer enrolled in a palliative care program treated at different centres in several countries. This adds to the generalizability of the findings. Second, we used an internationally validated instrument for screening for major depression[2]. Third, we used multivariate multilevel regression as method of analysis. This is a flexible and powerful method as it takes account of repeated measures, random error, clustering levels at specific settings and the simultaneous influence of several important clinical factors[3].

There are a number of potential limitations. In this study, the data were relatively sparse in the last weeks of life and there were no data available on potential important psychological determinants such as history of depression and the extent to which the patients has a supportive social network. Recruitment of centers was not at random but based on self-selection and most institutions were hospitals that provided anti-cancer treatment as part of their PC programmes[1]. In addition, sampling procedures between centers were not identical since some performed consecutive sampling, whereas others recruited a convenience sample. However, due to the large N in our study, we believe that the sampling strategy did not introduce a substantial bias, compared to other studies in PC or advanced cancer[4]. However, it cannot be ruled out that the frailest patients were not included.

8.3.2. Study 2: A mortality follow-back study among physicians of patients who died of cancer

To examine the use and timing of referral to specialist palliative care services and the reasons for not referring for patients with advanced cancer, we conducted a mortality follow-back study among physicians of patients who died of cancer (Chapter 3). This study is based on a representative sample of deaths in Flanders, Belgium, with a considerable response rate of 61%[5,6]. A major strength of this study is that by using death certificates, we were able to collect robust data for the entire population because a large sample of deaths was drawn across specialized palliative care settings[5]. This design is efficient for collecting generazible information about access to health care[7–9] and is a highly reliable method for describing end-of-life care[10–13]. Other studies in end-of-life care research are often limited in sample size or care settings which interferes with the chances of obtaining representative population data on end-of-life care[14,15]. The retrospective nature of this study design is also not hindered by problems of patient burden or non-response of the sickest patients, problems that are often found in prospective study designs[16]. Another strength of the present study is that the use of death certificates limits the biased selection of physicians compared to other end-of-life research where physicians can be selected on the basis of their interest in or attitudes towards end-of-life practices. This retrospective study design also limits the risk of influencing end-of-life practices[13].

Several limitations must be taken into account when interpreting the results. First, the physician signing the death certificate is sometimes not the patient's treating physician, and consequently is not in a position to fill out the questionnaire. Despite the instruction to transmit the questionnaire to the treating physician, in some cases the treating physician cannot be identified and hence data is unobtainable. Second, death certificates have to be processed by the proper authorities before they can be made available for research, which can lead to a considerable delay between the patient's death and the study of that death[13]. This increases the chance of recall bias. To address this issue, we encouraged physicians to fill in their questionnaires using the patient files, which are mostly readily at their disposal. Third, attending physicians will also not always have knowledge about palliative care services involved in another care setting, meaning that an underestimation of the use of specialized palliative care services cannot be excluded[17]. Last, relying on attending physicians as a proxy for reporting on reasons for not using palliative care may be less suitable for uncovering reasons emanating from patients or the family. This excluded the equally important perspectives of patients family and other caregivers[5,18]. However, death certificates in Belgium do not allow for the identification of the next of kin.

8.3.3. Study 3: A randomized controlled trial of the effect of early palliative care

The third study is a randomized controlled trial with the aim to assess whether early and systematic integration of palliative care has an impact on quality of life compared with usual care for advanced cancer patients (Chapters 4-7). This randomized controlled trial has several strengths. First, it was adequately powered to detect a reliable effect on quality of life; the actual dropout rate at 12 weeks was 5% less than expected. Second, patients were asked to complete two internationally well-validated questionnaires[19,20] to measure quality of life, enhancing the reliability of the results. Both instruments consistently showed improvements in quality of life, which adds to the robustness of our findings[21]. Third, a joint modeling approach was used to analyze quality of life of patients and their carers near death. This powerful and innovative statistical models allowed us to examine the long-term effects of early palliative care on quality of life while also taking into account survival of patients[22,23]. Last, a detailed description of usual care was provided, which allows for an in-depth understanding of the effects of integrating early and systematic palliative care in oncology care[24].

Several limitations exist with regards to the design of this trial. First, it was a single-centre study in a tertiary university hospital setting, therefore the findings might not be generalizable to other settings. Second, we cannot exclude a crossover effect; staff members were not masked to patient allocation to the intervention or control groups. Third, selection bias might affect the results. Patients were informed about the study using the term "palliative care", so it is likely that patients more open to palliative care participated in this trial. Fourth, as an exploratory study, many secondary endpoints were analyzed, such as the informal carer and end-of-life care data. Some endpoints may have reached significance by chance (type I error), which makes it difficult to draw firm conclusions. Fifth, we did not measure if the participating informal carers were present during the consultations. This limits our information on the direct impact of the intervention on the carers. Last, adherence to the protocol was lower than expected; we were not able to provide the pre-specified numbers of interventions, i.e. monthly consultations with the palliative care nurses and consultations every 3 months with the palliative care physician. However, the median number of palliative care consultations was 6 (IQR: 2- 11.5) in the early palliative care group compared to 0 (IQR 0-2) in usual care.

8.4. Discussion of the findings in the light of current challenges and state of affairs within palliative care research

This dissertation is based on successfully conducted studies in a population of vulnerable advanced cancer patients. In the section below, we will discuss the main findings of the studies in relation to the state of affairs within the existing literature.

8.4.1. Challenges of palliative care in oncology

Depression in specialized palliative care

A major finding in this dissertation is that more than half of advanced cancer patients enrolled in a palliative care program reported to suffer from symptoms of depression at some point in time during their disease trajectory (Chapter 2). This underlines the importance of careful and repeated examination of symptoms and psychosocial needs in oncology and palliative care settings. This is even more true since recent findings have shown that depression is a major contributor to poor quality of life in patients with advanced cancer[25,26]. However, it is important to note that screening positive for symptoms of depression does not represent a diagnosis of depression. Further clinical assessment is needed to differentiate between patients who are depressed versus patients who are emotionally distraught. We also found an overall decrease for symptoms of depression over time in patients who are cared for by multidisciplinary palliative care teams[1]. This could suggest that adding a multidisciplinary palliative care approach to regular oncology care diminishes symptoms of depression due to its more explicit and comprehensive attention to pain and symptom management, spiritual, psychological and social needs[27,28]. This is concurrent with recent data that early palliative care has a beneficial impact on depression of cancer patients in some countries[23,29–31].

Access to specialized palliative care

An important finding in this dissertation is the fact that the use of palliative care services in Belgium is high but still occurs late in the disease trajectory. This shows that the prevailing view on palliative care still follows a traditional dichotomous model of medical care, where palliative care is perceived as comfort care and offered when curative or disease-modifying treatment are no longer appropriate[32]. In addition, although patients with advanced cancer often suffer greatly from symptom burden[33–36], specialized palliative care services are not equally available to all these patients (Chapter 3). Patients with hematologic cancer have less chances of being referred to specialized palliative care services compared to patients with solid cancer. Physicians in our study reported that regular hematology care sufficiently addressed the patient's palliative care needs or perceived palliative care as not meaningful enough. It was also reported that patients refused

referral to palliative care. It is likely that lack of awareness by physicians and society of what palliative care can contribute to care is an important barrier of integration of palliative care in oncology[37–40].

8.4.2. Integrating specialized palliative care in oncology a timely manner

A significant effect on quality of life

Early integration of palliative care in oncology resulted in significant improvements in overall quality of life (Chapter 4-7). This was observed on the primary outcome of the trial, at 12 weeks (Chapter 5), but also later on at 18 weeks and shortly before death (Chapter 7). This is an important finding because it is indicative of a beneficial effect of early palliative care throughout the entire disease trajectory. This dissertation adds to the literature since our model (Chapter 4) is based on the landmark study with a physician-led intervention of Temel et al[29]. but was implemented with a nurse-led intervention in a setting where patients are standardly offered psychosocial support as part of usual oncology care[41]. This suggests that offering psychosocial care in oncology care alone is not enough, but that the additional support provided by a specialized palliative care team leads to further significant improvements in quality of life. One probable mechanism of this effect is the difference in focus and care delivery of the – multidisciplinary - oncology team and the palliative care team. Patients describe oncology clinics as being time-pressured and following a predictable structured pattern based on a particular management protocol[42,43]. While the focus of the oncology team is rightly more on treating the cancer, specialized palliative care teams look more at the whole person and less at the disease and are more directed by individual patient concerns[44]. The palliative care nurses in our trial provided emotional as well as physical support, devoted time to decision making and advanced care planning and provided support to the patient but also the broader family. It is likely that this extra layer of support that adds a patient-centered focus to the oncology care positively impacts the quality of life of patients.[45] There are, however, several other plausible mechanism of the benefit of early integration of palliative care. These will be discussed further in a later section of this discussion.

This dissertation also shows (Chapter 6) that introducing palliative care shortly after cancer diagnosis results in significant improvements in quality of life for informal carers even though this model of early palliative care is primarily designed for and directed at cancer patients and less at their carers. The carers show greater benefits in quality of life later in the disease trajectory (at three and one month prior to death of the patient) suggesting that while patients receive a direct benefit from early palliative care, their carers experience a positive subsequent effect. This may indicate that the patient-centered approach of early palliative care creates a powerful positive feedback loop in informal carers[46] .Our findings are consistent with the literature, many intervention with positive outcomes for family carers of patients with cancer are

primarily designed to address patient care, family carer wellbeing is often a secondary focus. A recent qualitative study, however, shows that caregivers describe their own quality of life to be closely linked to that of the patient. The study also demonstrated that taking on a new role as caregiver involved renegotiating their relationship with the patient and that caregiving affected them emotionally, socially, physically and financially[43]. Interventions that equally focus on the needs of cancer patients as well as on the needs of informal carers might lead enhanced health benefits for carers[47].

We have mainly discussed our findings in relation to the landmark study of Temel. However, a review by Haun et al.[24] in 2016 identified five trials of early palliative care which also showed positive effects on patient-reported outcomes. Since then, a RCT with benefits early palliative care for patients with lung and gastrointestinal cancer was also published. Table 1 gives a short description of these six trials and reports the main outcomes. It also shows the added value of our study: (1) unlike in the other trials, usual care already standardly offers psychosocial care for cancer patients, (2) positive results were found both on patient's and informal carer's quality of life and (3) it is the first European trial to find an effect in a heterogeneous cancer population.

Table 1: Overview of trials of early palliative care in cancer with positive outcomes

Authors	Country	Study population	Intervention	Usual Care	Outcomes*
Bakitas et al (2009)[31]	USA	Patients with advanced cancer with prognosis of approximately one year.	ENABLE II • Nurse-led intervention • Telephone-based consultations • Manual given to patient "Charting your course" with 4 topics: problem solving, communication and social support, symptom management and advanced care planning • Weekly for four weeks, then monthly follow up • Each session: distress thermometer • Shared Medical Appointments (SMA) by PC physician and nurse practitioner with patient and family carer Education • Nurse educators trained in problem solving / meetings with study staff / meetings with trainer and supervisor • SMA: trained by expert	Palliative care (PC) on demand : Supportive care specialists on demand	*Patient* **Quality of life (primary outcome)** Symptom Intensity **Mood** *Survival* *Informal Carer* N.A. *Resource use near end-of-life*
Bakitas et al (2015)[48,49]	USA	Advanced cancer patients with prognosis of approximately 6 months to 2 years – fast track design (3 months later)	ENABLE III • Initial in-person, outpatient PC consultation with PC physician • Six structured weekly telephone sessions by nurse • Manual patient "Charting Your Course" – extra: life-review approach • Monthly follow up calls Education • Nurse coach training: self-study, review of treatment manuals and scripts, role playing with feedback	PC on demand Supportive care specialists on demand	*Patient* Quality of life Symptom intensity Mood ***Survival*** *Informal carer* *Quality of life* **Mood** **Burden** *Resource use near end-of-life*
Maltoni et al. (2016)[50,51]	Italy	Patients with newly diagnosed metastatic pancreatic cancer	Systematic early palliative care: • Physician led-intervention • First: appointment with PC specialist with predefined checklist Then: follow up every 2 to 4 weeks until death	PC on demand	*Patient* **Quality of life (primary outcome)** Symptom intensity

		with a life expectancy of more than 2 months –	• All appointments based on General PC guidelines • Recommendations made by PC expert on decision making had to be shared by oncologist		Mood *Survival* *Informal Carer* *N.A.* ***Resource use near the end-of-life***
Temel et al. (2010)[27,29,52]	USA	Patients with metastatic non-small cell lung cancer	Early palliative care: • Interdisciplinary care • Meeting with member of PC team (nurse and physician) • At least monthly visits following the guidelines of the National Consensus Project for Quality PC • Special attention to physical and psychosocial symptoms, goals of care, assisting with decision making, coordination of care	PC on demand	*Patient* **Quality of life (primary outcome)** Symptom intensity **Mood** ***Survival*** *Informal Carer* *N.A.* ***Resource use near the end-of-life***
Zimmermann et al. (2014)[53,54]	Canada	Patients with advanced cancer with a prognosis of approximately 6 months to 2 years	Early palliative care: • Interdisciplinary approach (PC nurse and physician) • Outpatient o Routine visits monthly with routine structured symptom assessment o Attention to advanced care planning • Telephone-based follow up	PC on demand	*Patient* **Quality of life** **Symptom intensity** **Satisfaction with care** *Survival* *N.a.* *Informal Carer* Quality of life **Satisfaction with care** ***Resource use near the end-of-life***

Temel (2017[23,55])	USA	Patients with newly diagnosed incurable lung or non-colorectal gastrointestinal cancer	Early palliative care:
			• Interdisciplianry care
			  • Meeting with PC member (nurse or physician) within 4 weeks + at least monthly follow up
			  • Visits following the guidelines of National Consensus Project for Quality PC
			  • Telephone contact when in-person contact not possible
				PC on demand	*Patient*
					Quality of life
					Mood
					Prognostic understanding
					
					Survival
					N.a.
					
					Informal Carer:
					Quality of life
					Mood
					
					Resource use near the end-of-life
					N.a

*The outcomes for which a statistically significant effect of early palliative care was found are marked in bold.

Other effects of early and systematic integration of palliative care

Early and systematic palliative care also increases the number of consultations that patients have with psychologists. This could be due to increased direct referral by the palliative care nurses or due to their presence during the oncology staff meetings, also attended by the psychologists. Similar to other studies of early palliative care[29,53], our study showed only a small difference in physical functioning and only at the secondary 18 weeks endpoint. In addition, we found inconsistent effects on other functioning scales and symptom scales of the quality of life questionnaires. This indicates that quality of life is a broad construct, which can improve despite a relative lack of change in functioning or symptom burden[56,57].

This trial further shows that early and systematic integration of palliative care had no effect on the median overall survival of patients (Chapter 5). This contrasts with the result in the study of Temel et al[29] who found a benefit in survival for patient receiving early palliative care. Several mechanisms have been proposed for this survival advantage. Temel et al. suggested that the survival benefit could be related to the fact that patients in the intervention arm received less aggressive care compared to the control arm[45]. Chapter 6 shows that we did not find any differences in aggressiveness of end-of-life care between both groups which could have influenced the absence of effect in survival in our study. A possible explanation for these different outcomes is the intervention model. The role of the palliative care physician was more prominent in the Temel study compared to our nurse-led intervention. Research comparing physician-led to nurse-led interventions has shown that the latter have limited positive effect on mortality, hospitalization or readmission[58]. However, the ENABLE III trial, with fast-track design, did also observe a positive effect on survival but showed no significant effect in use of health care resources between both groups[48]. These findings suggest that palliative care provided soon after diagnosis confers a survival benefit by other mechanisms. Studies have examined the effect of treatment of depression and the administration of chemotherapy throughout the course of the disease on survival, but both did not account for the survival benefit for early palliative care[30,52]. Prospective research is needed to help understand the possible benefit in survival of early palliative care and to examine whether solid conclusion regarding a survival benefit of early palliative care can be claimed[24]. It might be, however, more interesting to note that there is no evidence that patients who received early palliative care tended to live less long compared to those whose care was directed at disease management alone. This implies that there should be no fear for shortening of life by making or accepting a referral to specialist palliative care services[45,59].

In Chapters 4 and 5 we found no effect of early palliative care on mood of patients or informal carers while four[23,29,31,48] out of six studies of early palliative care showed an improvement for cancer patients or their carers. This may be related to the fact that, as discussed in Chapter 4, usual care in Belgium is already multidisciplinary oriented which entails considerable attention for psychosocial needs[60]. This may limit the effect of additional psychosocial support offered by the palliative care team. However, although we did not find statistically significant effects, we generally observed a trend of less depression and anxiety for patients and their carers in the early palliative care group compared to usual care.

Mechanism of early integration of palliative care

The intervention of the randomized controlled trial, described in Chapter 4, is a complex intervention consisting out of several components: training of the palliative care team, semi-structured consultations primarily with palliative care nurses, structured symptom assessment and integration of palliative care in oncology. This raises the concern which are the core components that lead to better patient-reported and carer- reported outcomes[61,62]. The design of our trial doesn't allow us to make clear conclusions but we will address some plausible mechanisms that might be of influence. When we look at which topics were discussed during the consultations in the first 18 weeks, we see that symptom management (32%) and illness understanding (29%) were discussed the most. This might suggest that systematically addressing symptom management, which also entails symptom assessment, and illness understanding are the most important determinants of the improvement in quality of life. A recent study examining the determinants of early palliative care showed that the focus of palliative care clinicians during visits is associated with different outcomes: focusing on coping during consultations was associated with better quality of life, while visits that focused more on treatment decisions and advanced care planning were associated with higher quality of end-of life care.[63]

Another potential important determinant could be related to the systematic approach included in this model as opposed to an on-demand intervention, mostly due to oncologist-driven referral, in usual care[50]. Palliative care consultations were planned on a structured basis, starting early in the disease trajectory. This gives patients and their carers the opportunity to develop a long-standing relationship with the members of the palliative care team, as opposed to usual care where the members of the PC team are contacted late in the disease trajectory. Building up trust might facilitate difficult conversations regarding prognosis or the discussion of treatment options that align with the goals of care of patients and their informal carers[42,62,64].

A third plausible mechanism is that patients simply perceive oncology and palliative care to be discrete and complementary, both contributing to comprehensive care. On the one hand, palliative care teams have the

role and credibility to assist patients and their families in managing their symptoms, providing psychosocial and spiritual support and discussing goals of care[42,65]. Oncologists, on the other hand, have the role to focus on how to direct cancer therapy, to stabilize the disease and to prolong life[45,66]. It is possible that patients and their carers may filter their concerns regarding symptoms, disease burden for the oncology team out of fear that they may give up on them[28]. The additional support of an independent team specialized in proving holistic and patient-centered care might provide a natural opportunity for patients and their carers to clarify questions about prognosis and openly discuss their fears, concerns, symptom burden and treatment wishes[42,44].

The literature also suggest that increasing the skills of patients to cope with their life threatening disease might be a potential mechanism of early palliative care. A recent study of early palliative care showed that the intervention increased the use of an approach-oriented coping style in patients, as opposed to avoidant coping, and showed that these changes in coping style accounted for improvements in patient's quality of life[67].

Is this integration?

In this dissertation (Chapter 3), we described four components of our intervention, one of which is the integration component. This component meant that the palliative care nurses not only performed semi-structured consultations but also (1) attended oncology staff meetings, (2) reported in electronic patient files and (3) contacted the members of the oncology team personally to discuss specific needs of patients when deemed necessary. We have received some criticism of labeling our model as an integration model[68]. It was argued, based upon a definition of integration by Leutz[69], that our intervention fits most with the lowest level of integration which is described as 'linkage'. Linkage as concept of integration entails a basic and common understanding of the various professionals' skills by both teams. This also means that patients are cared for in a planned system, based on understanding of special needs, but that the work between both teams is done in parallel or in series. We would like to argue that our intervention achieved more than teams working in parallel. We rather see our model as a comanagement model[70]. Comanagement describes the close clinical collaboration between the palliative care specialist and the primary clinician in delivering patient care in the hospital setting. While each member provides input in managing different aspects of treatment, overall responsibility lies with the primary/referring clinician[70]. The fact that our model is more than merely linkage is also reflected by the increase in consultations by the psychologists of the oncology team. However, we agree with the authors that there is room for improvement in our model regarding integration[68].

8.5. Recommendations for research, policy and practice

Our findings suggest that there is room for improvement in the timing and content of specialized palliative care for patients with advanced cancer. Based on the studies in this dissertation, there are some important recommendations for research, clinicians and policy makers regarding the initiation and provision of specialized palliative care in oncology.

8.5.1. Implications for research

Several recommendations can be made for future research and some of these are described below.

Introducing palliative care services soon after diagnosis for patients with advanced cancer helps to enhance patients' quality of life in the hospital setting. However, further research is needed to elucidate the mechanisms by which palliative care interventions lead to these effects. Many question remain: What is the optimal content of early palliative care? Are models with less frequent consultations equally beneficial for patients? What is the ideal level of integration?[68] How is palliative care that is offered early in the disease different from palliative care that is offered late in the disease trajectory? We observed also observed high prevalence of symptoms of depression in palliative cancer care. Could palliative care provide by an interdisciplinary team, with psychologists and psychiatrists that provide support in psychological assessment, improve outcomes of quality of life and symptom control? These questions can be answered with qualitative as well as quantitative research methods. Further studies that adapt and apply novel models of early palliative care integrated in the full continuum of care settings (home, nursing home, and hospital) and address these challenges are needed.

Although several studies have noted beneficial effects on caregivers' outcomes, the mechanism by which early integration of palliative care impacts these outcomes remains unknown. Caregivers may have benefited from their direct interaction with the specialized palliative care team. Alternatively, improvement in patient-reported outcomes with early integrated palliative care may have led to an amelioration of quality of life in caregivers[43,54,55]. Future studies should be adequately powered to better assess contributing factors of the effect of early integrated PC on caregiver outcomes given their critical role in providing care and support for patients with advanced cancer. We believe that future interventions should be directed both at patients and caregivers, since interventions directed only at caregivers may not always be practical in the context of advanced cancer, due to the time commitment and cost they often entail [47].

This dissertation shows that patients with hematologic malignancies have less chances of being referred to specialized palliative care and if referred, this only occurs late in the disease trajectory. Unfortunately, patients with hematologic malignancies are also known to have substantial illness burden and poor quality of life. While it was shown that early palliative care benefits patients with advanced solid cancer, the effect in patients with hematologic malignancies is still unknown since most early palliative care trials did not include this patient population. Robust studies of early palliative care, utilizing validated measures to assess patient reported outcomes, survival, and health services utilization in this patient population are needed.

8.5.2. Implications for policy

Rebranding of palliative care

We have shown that early palliative care can improve patient outcomes and caregiver outcomes and thus the importance of the timely referral to specialized palliative care should be underlined. We have also found that attitudes of physicians are barriers to referral to specialized palliative care. Contrary to what is often believed, palliative care is more than end-of-life care and can be provided alongside treatments targeting the underlying disease[37].

When conducting the randomized controlled trial described in chapter 4, we asked oncologists to introduce the term 'palliative care' to advanced cancer patients much earlier in the disease trajectory compared to clinical practice. Initially, oncologists were reluctant to this idea, mostly out of fear of taking away the hope of patients and their loved ones and because of negative perceptions of patients toward palliative care. We were, however, successful in including patients because of our efforts of how we portrayed palliative care. Negative attitudes toward palliative care are also cited in research and a change of name to 'supportive care' has been proposed[14,38,71,72]. One study observed earlier outpatient referral from oncologists after changing the name of the service to supportive care[73]. Another study in patients and their caregivers showed that they felt a stigma associated with the term palliative care and felt that rebranding palliative care could be helpful[74].

We believe, together with the authors of other studies, that improving the awareness in society of the role of modern palliative care is key for cancer patients to receive comprehensive cancer care. This dissertation and other studies have shown that palliative care is more than end-of-life care and that patients who receive concurrent palliative care tend to live at least as long as those whose care is directed at disease management alone[31,53,75]. Hence, there should not be fear of shortening life by making or accepting referral to specialized palliative care. There is a need to "rebrand" palliative care and this should be done by focusing on the benefits of early integration of palliative care[76]. This rebranding needs to include administrators and politicians since too many people who can have a positive impact on health

care resources for palliative care still do not understand modern palliative care. In addition, a broad based education program for the public and patients is necessary to ensure better understanding of what palliative care stand for and entails[37].

Training and education

We believe that developing training programs for clinicians in early integrated palliative care are needed since early palliative care requires some different strategies compared to inpatient palliative care consults. Inpatient palliative care consults are mostly driven by specific demands such as complex symptom control while early palliative care unfolds over a longer period of time and does not always involve a clinical urgency. Thus this new model of care requires that palliative care specialists, experienced and trained in inpatient palliative care, shift their strategies when working with early palliative care patients[44]. The early palliative care approach is more about guiding patients and their carers over time and including frequent and structured symptom assessment instead of conducting discussion of goals of care at a turning point in the patients' illness. It has been suggested that training will need to address unlearning of typical approaches that are highly functional for inpatient palliative care such as the crisis mentality and that education programs should include communication and counseling skills that support coping, planning, and acceptance; and collaborating with other specialists such as oncologists[44].

Resources

Because of government funding, specialised palliative care teams are available free of charge in hospitals in Belgium[77]. However, palliative care is one of the fastest growing subspecialties in medicine in the past decade[37] and our recommendation to implement early integrated palliative care in oncology adds to the increasing demands. Even though, specialized palliative care is relatively well available in Belgium, administrators and politicians should continue to invest in these services and provide adequate resources and infrastructure for early integration of palliative care in oncology as part of routine clinical practice.

8.5.3. Implications for practice

On the basis of the findings of this dissertation, recommendations can be made to improve integration of specialized palliative care in oncology and enhance screening form symptoms of depression in this setting. These recommendations are listed below and specifically directed at oncologists and specialized palliative care team working in the hospital. This guideline adaptation pertains to adults (age 18 years and older) with advanced cancer. Of course, palliative care can also be delivered to other patient groups and by health care professionals who do not specialize in palliative care. However, such recommendations are beyond the scope of this dissertation.

Screening of depression

There is consensus in the literature that it is recommended to screen all patients with cancer for symptoms of depression at their initial visit and periodically thereafter across the trajectory of care. Screening should be performed using validated measures such as the PHQ-2[2]. Depending on levels of symptoms reported (cut-off score > 2), international guidelines suggest that the remaining items of the PHQ-9 should be completed. If moderate to severe or severe symptomatology is detected through screening, individuals should have further diagnostic assessment to identify the extent of the depressive symptoms and the presence or absence of a mood disorder[78].

Integration of specialized palliative care in oncology

Our findings suggest that there is room for improvement in the timing and integration of specialized palliative care in oncology. Chapter 3 shows that referral to specialized palliative care still occurs late in the trajectory and chapters 4 to 7 underline the importance and beneficial effects of early palliative care.

Below we discuss some guidelines and facilitation factors for the implementation of an early palliative care approach in oncology:

- Identifying patients for referral: Oncologists and specialists in palliative care should develop guidelines together about the cancer patients that are, at a defined point in their disease, appropriate for early referral. Most trials of early palliative care used prognosis as time-based criterion for referral. In this dissertation, a heterogeneous group of patients with advanced cancer with a life expectancy of approximately 12 months (assessed by the treating oncologist) were eligible for early palliative care. We believe that standardized referral criteria can complement clinical judgment to facilitate appropriate referral[79]. However, referral criteria should also be tailored individual hospital setting, according to the resources which are available[28].

- Treating oncologist as advisor: The oncology team should offer patients information about the benefits of involvement of palliative care on quality of life and symptoms. Oncologists should advise patients and carers that palliative care specialists form part of the care team and that they will have structural consultations with those specialists to manage symptoms and enhance their quality of life while receiving cancer treatment.

- Structured consultation by the palliative care team: The literature has reported benefits of early palliative care for patients which is provided in a structured manner as opposed to palliative care on demand. This

dissertation shows that it is important to organize palliative care consultations, which entail routine symptoms assessment, when patient have an approximate life expectancy of 12 months, which is soon after diagnosis of advanced disease for several patients, and in periodic times across the trajectory of care.

- Attention to informal carers: There is general consensus in the literature that patients and informal carers react to cancer as a unit and that both have needs for help from health professionals[47]. Clinician should be aware that carers also likely to benefit from early and systematic palliative care and to achieve optimal comprehensive cancer care, the care plan should focus on these patient-carer units.

- Integration of palliative care team: We were able to demonstrate a benefit on patients' and caregivers' quality of life based on a model of palliative care where palliative care team members were present during multidisciplinary staff meetings. Hence, we and other authors advise that a member of the palliative care team should be included in multidisciplinary case conferences and tumour boards of the oncology team[39].

References

1 Hjermstad MJ, Aass N, Aielli F, *et al.* Characteristics of the case mix, organisation and delivery in cancer palliative care: a challenge for good-quality research. *BMJ Support Palliat Care* 2016; **0**: 1–12.

2 Kroenke K, Spitzer RL, Williams JBW. The patient health questionnaire-2: Validity of a two-item depression screener. *Med Care* 2003; **41**: 1284–92.

3 Ekström M, Johnson MJ, Schiöler L, Kaasa S, Hjermstad MJ, Currow DC. Who experiences higher and increasing breathlessness in advanced cancer? The longitudinal EPCCS Study. *Support Care Cancer* 2016; **24**: 3803–11.

4 Stone PC, Gwilliam B, Keeley V, Todd C, Kelly LC, Barclay S. Factors affecting recruitment to an observational multicentre palliative care study. *BMJ Support Palliat Care* 2013; **3**: 318–23.

5 Beernaert K, Deliens L, Pardon K, *et al.* What Are Physicians' Reasons for Not Referring People with Life-Limiting Illnesses to Specialist Palliative Care Services? A Nationwide Survey. *PLoS One* 2015.

6 Verkissen MN, Houttekier D, Cohen J, Schots R, Chambaere K, Deliens L. End-of-life decision-making across cancer types: results from a nationwide retrospective survey among treating physicians. *Br J Cancer* 2018; : 1–8.

7 Barnato A, Lynn J. Response: Resurrecting treatment histories of dead patients. *Jama* 2005; **293**: 1591.

8 Teno JM, Mor V. Response: Resurrecting treatment histories of dead patients. *Jama* 2005; **293**: 1591.

9 Rosenwax LK, McNamara B a. Who receives specialist palliative care in Western Australia--and who misses out. *Palliat Med* 2006; **20**: 439–45.

10 van der Heide A, Deliens L, Nilstun T, *et al.* End-of-life decision-making in six European countries:descriptive study. *Lancet* 2003; : 1–6.

11 Bilsen J, Cohen J, Chambaere K, *et al.* Medical End-of-Life Practices under the Euthanasia Law in Belgium. *N Engl J Med* 2009; **361**: 1120–1.

12 Chambaere K, Vander Stichele R, Mortier F, Cohen J, Deliens L. Recent trends in euthanasia and other end-of-life practices in Belgium. *N Engl J Med* 2015; **372**: 1179–81.

13 Chambaere K, Bilsen J, Cohen J, *et al.* A post-mortem survey on end-of-life decisions using a representative sample of death certificates in Flanders, Belgium: research protocol. *BMC Public Health* 2008; **8**: 299.

14 Hui D, Kim S-H, Kwon JH, *et al.* Access to palliative care among patients treated at a comprehensive cancer center. *Oncologist* 2012; **17**: 1574–80.

15 Fadul N, Elsayem A, Palmer JL, Zhang T, Braiteh F, Bruera E. Predictors of access to palliative care services among patients who died at a Comprehensive Cancer Center. *J Palliat Med* 2007; **10**: 1146–52.

16 Earle CC, Ayanian JZ. Looking back from death: The value of retrospective studies of end-of-life care. *J Clin Oncol* 2006; **24**: 838–40.

17 Dierickx S, Deliens L, Cohen J, Chambaere K. Involvement of palliative care in euthanasia practice in a context of legalized euthanasia: A population-based mortality follow-back study. *Palliat Med* 2018; **32**: 114–22.

18 Catt S, Blanchard M, Addington-Hall J, Zis M, Blizard R, King M. Older adults' attitudes to death, palliative treatment and hospice care. *Palliat Med* 2005; **19**: 402–10.

19 Fayers P, Bottomley A. Quality of life research within the EORTC—the EORTC QLQ-C30. *Eur J Cancer* 2002; **38**: 125–33.

20 Cohen SR, Mount BM, Bruera E, Provost M, Rowe J, Tong K. Validity of the McGill Quality of Life Questionnaire in the palliative care setting: a multi-centre Canadian study demonstrating the importance of the existential domain. *Palliat Med* 1997; **11**: 3–20.

21 Albers G, Echteld MA, de Vet HC, Onwuteaka-Philipsen BD, van der Linden MH, Deliens L. Evaluation of quality-of-life measures for use in palliative care: a systematic review. *Palliat Med* 2010; **24**: 17–37.

22 Li Z, Frost HR, Tosteson TD, *et al.* A semiparametric joint model for terminal trend of quality of life and survival in palliative care research. *Stat Med* 2017; **36**: 4692–704.

23 Temel JS, Greer JA, El-jawahri A, *et al.* Effects of Early Integrated Palliative Care in Patients With Lung and GI Cancer : A Randomized Clinical Trial. *J Clin Oncol* 2017; : 1–17.

24 Haun MW, Estel S, Rücker G, *et al.* Early palliative care for adults with advanced cancer (Review). *Cochrane Database Syst Rev* 2017; : 1–105.

25 Kelly C, Paleri V, Downs C, Shah R. Deterioration in quality of life and depressive symptoms during radiation therapy for head and neck cancer. *Otolaryngol - Head Neck Surg* 2007; **136**: 108–11.

26 Grotmol KS, Lie HC, Hjermstad MJ, *et al.* Depression - a major contributor to poor quality of life in patients with advanced cancer. *J Pain Symptom Manage* 2017; **54**: 889–97.

27 Pirl WF, Greer JA, Traeger L, *et al.* Depression and survival in metastatic non-small-cell lung cancer: effects of early palliative care. *J Clin Oncol* 2012; **30**: 1310–5.

28 Hui D, Bruera E. Integrating palliative care into the trajectory of cancer care. Nat. Rev. Clin. Oncol. 2016; **13**: 159–71.

29 Temel JS, Greer J a, Muzikansky A, *et al.* Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010; **363**: 733–42.

30 Pirl WF, Greer JA, Traeger L, *et al.* Depression and survival in metastatic non-small-cell lung cancer: effects of early palliative care. *J Clin Oncol* 2012; **30**: 1310–5.

31 Bakitas M, Lyons K, Hegel M, *et al.* The Project ENABLE II Randomized Controlled Trial to Improve Palliative Care for Patients with Advanced Cancer. *J Am Med Assoc* 2009; **302**: 741–9.

32 Lynn J, Adamson DM. Living Well at the End of Life: Adapting Health Care to Serious Chronic Illness in Old Age. *Rand Heal* 2003; : 1–22.

33 Manitta VJ, Philip JAM, Cole-Sinclair MF. Palliative Care Review Palliative Care and the Hemato-Oncological Patient: Can We Live Together? A Review of the Literature. *J Palliat Med* 2010; **13**: 1021–5.

34 Teunissen SCCM, Wesker W, Kruitwagen C, de Haes HCJM, Voest EE, de Graeff A. Symptom Prevalence in Patients with Incurable Cancer: A Systematic Review. *J Pain Symptom Manage* 2007; **34**: 94–104.

35 Laugsand EA, Kaasa S, de Conno F, Hanks G, Klepstad P, of the EAPC [Collective Name]. Intensity and treatment of symptoms in 3,030 palliative care patients: a cross-sectional survey of the EAPC Research Network. *J Opioid Manag* 2009; **5**: 11–21.

36 LeBlanc TW, El-Jawahri A. When and why should patients with hematologic malignancies see a palliative care specialist? *ASH Educ Progr B* 2015; **2015**: 471–8.

37 Zhi WI, Smith TJ. Early integration of palliative care into oncology: evidence, challenges and barriers. *Ann Palliat Med* 2015; **4**: 122–31.

38 Leblanc TW, O 'donnell JD, Crowley-Matoka M, *et al.* Perceptions of Palliative Care Among Hematologic Malignancy Specialists: A Mixed-Methods Study. *J Oncol Pract* 2015; **11**: 230–8.

39 Kain DA, Eisenhauer EA. Early Palliative Care for Patients with Advanced Cancer. *Curr Oncol* 2016; **23**: 374–7.

40 Zimmermann C, Swami N, Kryzanowska M, *et al.* Perceptions of palliative care among patients with advanced cancer and their caregivers. *CMAJ* 2016; **188**.

41 Van Belle S. How to implement the multidisciplinary approach in prostate cancer management: The Belgian model. *BJU Int* 2008.

42 Hannon B, Swami N, Pope A, *et al.* Early Palliative Care and Its Role in Oncology: A Qualitative Study. *Oncologist* 2016; **21**: 1387–95.

43 McDonald J, Swami N, Pope A, *et al.* Caregiver quality of life in advanced cancer: Qualitative results from a trial of early palliative care. *Palliat Med* 2018; **32**: 69–78.

44 Back AL, Park ER, Greer JA, *et al.* Clinician Roles in Early Integrated Palliative Care for Patients with Advanced Cancer : *J Palliat Med* 2014; **17**: 1244–8.

45 Greer JA., Jackson VA, Meier DE, Temel JS. Early Integration of Palliative Care Services With Standard Oncology Care for Patients With Advanced Cancer. *CA Cancer J Clin* 2013; **63**: 349–63.

46 Fuerst ML. Early palliative care improves outcomes for family caregivers. *Oncol Times* 2016; **38**: 13.

47 Northouse LL, Katapodi MC, Song L, Zhang L, Mood DW. Interventions with family caregivers of cancer patients: meta-analysis of randomized trials. *CA Cancer J Clin* 2010; **60**: 317–39.

48 Bakitas MA, Tosteson TD, Li Z, *et al.* Early Versus Delayed Initiation of Concurrent Palliative Oncology Care : Patient Outcomes in the ENABLE III Randomized Controlled Trial. *J Clin Oncol* 2015; **33**: 1438–1145.

49 Dionne-Odom JN, Azuero A, Lyons KD, *et al.* Benefits of Early Versus Delayed Palliative Care to

Informal Family Caregivers of Patients With Advanced Cancer: Outcomes From the ENABLE III Randomized Controlled Trial. *J Clin Oncol* 2015; **33**: 1446–52.

50 Maltoni M, Scarpi E, Dall M, *et al.* Systematic versus on-demand early palliative care : results from a multicentre , randomised clinical trial. *Eur J Cancer* 2016; **65**: 61–8.

51 Maltoni M, Scarpi E, Dall'Agata M, *et al.* Systematic versus on-demand early palliative care: A randomised clinical trial assessing quality of care and treatment aggressiveness near the end of life. *Eur J Cancer* 2016; **69**: 110–8.

52 Greer J a., Pirl WF, Jackson V a., *et al.* Effect of early palliative care on chemotherapy use and end-of-life care in patients with metastatic non-small-cell lung cancer. *J Clin Oncol* 2012; **30**: 394–400.

53 Zimmermann C, Swami N, Krzyzanowska M, *et al.* Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. *Lancet* 2014; : 1721–30.

54 Mcdonald J, Swami N, Hannon B, *et al.* Impact of early palliative care on caregivers of patients with advanced cancer: cluster randomised trial. *Ann Oncol* 2017; **28**: 163–8.

55 El-Jawahri A, Greer JA, Pirl WF, *et al.* Effects of Early Integrated Palliative Care on Caregivers of Patients with Lung and Gastrointestinal Cancer: A Randomized Clinical Trial. *Oncologist* 2017; : theoncologist.2017-0227.

56 Smith KW, Avis NE, Assmann SF. Distinguishing between quality of life and health status in quality of life research: A meta-analysis. *Qual Life Res* 1999; **8**: 447–59.

57 Carr AJ, Higginson IJ. Are quality of life measures patient centred? *BMJ* 2001; **322**: 1357–60.

58 Lewis R, Neal RD, Williams NH, *et al.* Nurse-led vs. conventional physician-led follow-up for patients with cancer: systematic review. *J Adv Nurs* 2009; **65**: 706–23.

59 Hawley P. Barriers to Access to Palliative Care. *Palliat Care* 2017; **10**.

60 Van Belle S. How to implement the multidisciplinary approach in prostate cancer management: the Belgian model. *BJU Int* 2008.

61 Gaertner J, Siemens W, Meerpohl JJ, *et al.* Effect of specialist palliative care services on quality of life in adults with advanced incurable illness in hospital, hospice, or community settings: systematic review and meta-analysis. *Bmj* 2017; : j2925.

62 Jacobsen J, Jackson V, Dahlin C, *et al.* Components of early outpatient palliative care consultation in patients with metastatic nonsmall cell lung cancer. *J Palliat Med* 2011; **14**: 459–64.

63 Hoerger M, Greer JA, Jackson VA, *et al.* Defining the elements of early palliative care that are associated with patient-reported outcomes and the delivery of end-of-life care. *J Clin Oncol* 2018; **36**: 1096–102.

64 Fadul NA, Osta E, Dalal S, Poulter VA, Bruera E. Comparison of Symptom Burden among Patients Referred to Palliative Care with Hematologic Malignancies versus those with Solid Tumors. *J Palliat Med* 2008; **11**: 422–7.

65 Yoong J, Park ER, Greer J a, *et al.* Early palliative care in advanced lung cancer: a qualitative study. *JAMA Intern Med* 2013; **173**: 283–90.

66 Bauman JR, Temel JS. The Integration of Early Palliative Care With Oncology Care : The Time Has Come for a New Tradition. *J Natl Compr Cancer Netw* 2014; **12**: 1763–71.

67 Greer JA, Jacobs JM, El-Jawahri A, *et al.* Role of patient coping strategies in understanding the effects of early palliative care on quality of life and mood. *J Clin Oncol* 2018; **36**: 53–60.

68 Kaasa S, Loge JH. Early integration of palliative care—new evidence and old questions. *Lancet Oncol* 2018; **19**: 280–1.

69 Leutz W.N. Five Laws For Integrating Medical and Social Services: Lessons from the United States and the United Kingdom. *Milbank Q* 1999; **77**: 77–110.

70 Bruera E, Hui D. Integrating Supportive and Palliative Care in the Trajectory of Cancer: Establishing Goals and Models of Care. *J Clin Oncol* 2010; **28**: 4013–7.

71 Hui D, Park M, Liu D, Reddy A, Dalal S, Bruera E. Attitudes and beliefs toward supportive and palliative care referral among hematologic and solid tumor oncology specialists. *Oncologist* 2015; **20**: 1–7.

72 Fadul N, Elsayem A, Palmer JL, *et al.* Supportive versus Palliative care: What's in a name? *Cancer* 2009; **115**: 2013–21.

73 Dalal SL, Palla R, Chacko L, Nguyen NA, Fadul ZL, Bruera E. Impact of the change in service name from 'palliative' to 'supportive' care on patient referral at a comprehensive cancer center. *J Clin Oncol* 2010; **28**. http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/9052.

74 Zimmermann C, Swami N, Krzyzanowska M, *et al.* Palliative care: Renaming as supportive care and integration into comprehensive cancer care. *CMAJ* 2016; **188**: 711–2.

75 El-Jawahri A, Greer JA, Pirl WF, *et al.* Effects of early integrated palliative care in patients with lung and gi cancer: A randomized clinical trial. *Oncologist* 2017; **35**: 834–41.

76 Berry LL, Castellani R, Stuart B. The Branding of Palliative Care. *J Oncol Pract* 2016; **12**: 48–50.

77 Federale Evaluatiecel Palliatieve Zorg. Evaluatierapport palliatieve zorg. 2014 http://leif.be/data/Wetgeving/Rapporten/Evaluatierapport_palliatieve_zorg_2014.pdf.

78 Andersen BL, DeRubeis RJ, Berman BS, *et al.* Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: An American Society of Clinical Oncology guideline adaptation. *J Clin Oncol* 2014; **32**: 1605–19.

79 Hui D, Meng Y-C, Bruera S, *et al.* Referral Criteria for Outpatient Palliative Cancer Care: A Systematic Review. *Oncologist* 2016; **21**: 895–901.

Samenvatting van de belangrijkste bevindingen

Inleiding

Patiënten met geavanceerde en ongeneeslijke kanker lijden doorgaans aan een groot aantal ernstige symptomen. Pijn, vermoeidheid, misselijkheid/braken, dyspnoe, constipatie, verlies van eetlust en depressie behoren tot de meeste voorkomende symptomen. Deze symptomen zijn echter vaak onderbehandeld en ondergediagnosticeerd. Mogelijke redenen hiervoor zijn de beperkte tijd die beschikbaar is om patiënten te verzorgen, de nadruk op genezing en levensverlenging in plaats van kwaliteit van leven en een gebrek aan expertise in symptoommanagement. Oncologen staan centraal in de zorg voor patiënten maar door het toenemend aantal mensen die gediagnosticeerd worden met kanker en de complexiteit van kankertherapieën blijven de eisen voor oncologen stijgen. Zij krijgen de veeleisende taak om behandelingsopties en mogelijke bijwerkingen volledig en duidelijk te bespreken en gelijktijdig ook voldoende tijd en aandacht te besteden aan de talrijke zorgbehoeften, het ziekte-inzicht en de behandeldoelen van mensen met kanker.

Recent werd gesuggereerd dat integratie van gespecialiseerde palliatieve zorg in de oncologische zorg een aantal van deze beperkingen in het huidige traditionele model van oncologische zorg kan aanpakken. De Wereldgezondheidsorganisatie (WHO) omschrijft palliatieve zorg als "*een benadering die de kwaliteit van leven verbetert van mensen met een levensbedreigende aandoening en hun families door preventie en verlichting van lijden door middel van vroege identificatie en assessment van pijn en andere problemen van fysieke, psychosociale en spirituele aard*". De WHO benadrukt dat palliatieve zorg van toepassing is vroeg in het ziektetraject, samen met andere therapieën die als doel hebben om te genezen of het leven te verlengen, zoals chemotherapie of radiotherapie. Vandaag de dag worden patiënten echter nog steeds vaak (te) laat doorverwezen naar gespecialiseerde palliatieve zorg, kort nabij de dood.

Er is meer en meer wetenschappelijke evidentie beschikbaar dat dit nieuw model van vroege doorverwijzing naar gespecialiseerde palliatieve zorg in combinatie met oncologische zorg ondersteunt maar het nieuwe model heeft ook nog een aantal tekortkomingen.

Ten eerste, onderzoek naar doorverwijzing naar gespecialiseerde palliatieve zorg beschouwde kankerpatiënten vaak als een homogene groep van patiënten of beperkten zich tot patiënten uit een bepaald gezondheidssetting of instituut (vb. enkel de ziekenhuissetting). Om een goed begrip te hebben van het niveau van integratie van palliatieve zorg in de oncologie is er een nood naar onderzoek op populatieniveau. Vele studies zijn ook gericht op de symptoomlast van mensen met kanker en depressie is een veelvoorkomende en frequent onderzocht symptoom. Huidige studies over depressie en kanker beperken zich echter vaak tot één bepaalde setting, zoals bijv. oncologie of palliatieve zorg en zijn in opzet vaker cross-sectioneel van aard en niet longitudinaal. Er zijn weinig studies die de ontwikkeling van depressie

onderzoeken bij mensen met kanker die ook palliatieve zorg krijgen. Dergelijke studies zijn van belang om een beter begrip te hebben van de veranderende klachten van depressie over tijd en kunnen lijden tot betere symptoombestrijding.

Ten tweede, bij de aanvang van deze doctoraatsstudie waren er weinig studies beschikbaar die het effect nagingen van het nieuwe model van vroege integratie van gespecialiseerde palliatieve zorg in de oncologie in Europa. Het grote merendeel aan onderzoek situeerde zich in Noord Amerika. Hoewel deze resultaten veelbelovend bleken te zijn was er nood aan meer onderzoek, ook uit Europa, om de vertaalslag van dit nieuwe model te kunnen maken naar de klinische praktijk.

Het hoofddoel van dit proefschrift is om inzicht te verwerven in de uitdagingen en voordelen van de integratie van palliatieve zorg in de oncologische zorg. We zullen ons richten op (1) symptoomlast bij gevorderde kankerpatiënten, specifiek voor depressie, (2) op de verschillen in inzet van gespecialiseerde palliatieve zorg tussen verschillende kankertypes en (3) op het effect van vroege en systematische integratie van palliatieve zorg in de oncologische zorg in België. Dit proefschrift richt zich op patiënten met vergevorderde kanker en hun naasten.

Onderzoeksvragen

In dit proefschrift hebben we getracht om de volgende onderzoeksvragen te beantwoorden ondergebracht in drie doelen:

Het **eerste doel** is om de uitdagingen van de palliatieve zorg in de oncologie te onderzoeken met betrekking tot symptoom assessment en doorverwijzing naar gespecialiseerde palliatieve zorg;

1) Wat is de prevalentie van symptomen van depressie en wat zijn gerelateerde factoren in een grote steekproef van kankerpatiënten die deelnamen aan een palliatief zorgprogramma?
2) Zijn er verschillen tussen kankertypes in het gebruik en de timing van verwijzing naar gespecialiseerd palliatieve zorg en wat zijn de redenen voor niet-verwijzing?

Het **tweede doel** is om het onderzoeksprotocol van een gerandomiseerde gecontroleerde studie van vroege en systematisch integratie van palliatieve zorg in de oncologie te beschrijven in de Belgische gezondheidszorg.

Het **derde doel** is om het effect van vroege en systematische integratie van palliatieve zorg in de oncologie te onderzoeken aan de hand van de volgende onderzoeksvragen:

1) Wat is het effect van vroege en systematische integratie van palliatieve zorg in de oncologie voor patiënten met geavanceerde kanker kort na diagnose?
2) Wat is het effect van vroege en systematische integratie van palliatieve zorg in de oncologie op mantelzorgers van patiënten met gevorderde kanker?
3) Wat is het effect van vroege en systematische integratie van palliatieve zorg in de oncologie op zorg aan het levenseinde en kwaliteit van leven van patiënten nabij de dood?

Methodes

Om de onderzoeksvragen van dit proefschrift te beantwoorden, werden drie verschillende methodes van gegevensverzamelingen gebruikt. We gebruikten een prospectieve cohortstudie om de prevalentie en variabiliteit van symptomen van depressie te beoordelen bij kankerpatiënten die deelnamen aan een programma voor palliatieve zorg (hoofdstuk 1). Vervolgens maakten we gebruik van een studie die peilt naar zorg aan het levenseinde, inclusief doorverwijzing naar gespecialiseerde palliatieve zorg, op basis van een representatieve steekproef van officiële overlijdensakten om de verschillen in gebruik en timing van gespecialiseerde palliatieve zorg binnen kanker te onderzoeken (Hoofdstuk 2). Ten laatste hebben we een gerandomiseerd gecontroleerde studie uitgevoerd in het Universitair Ziekenhuis (UZ) Gent om de effecten van vroege en systematische integratie van palliatieve zorg in de oncologie te onderzoeken (Hoofdstuk 3 tot 6).

Deze drie methoden worden in de volgende paragrafen beschreven.

Studie 1: Een internationale prospectieve cohortstudie bij kankerpatiënten in een palliatief zorgprogramma (hoofdstuk 2)

We gebruikten gegevens uit de " European Palliative Care Cancer Symptom (EPCCS). Dit is een internationaal, multi-centrum, prospectieve studie in een populatie van mensen met kanker die palliatieve zorg krijgen. Deze studie werd uitgevoerd in 30 centra in 12 landen tussen april 2011 en oktober 2013. Het bestond uit een online vragenlijst over de organisatie van palliatieve zorg en uit maandelijkse vragenlijsten die naar symptoomlast peilen bij patiënten en artsen uit elk centra. Deze vragenlijsten werden ingevuld op baseline en vervolgens maandelijks t.e.m. 6 maand na inclusie, tot overlijden of tot weigering van verdere deelname. Op baseline werden demografische gegevens, zoals datum van diagnose van kanker, comorbiditeit, leeftijd enz. verzameld. Bij elke assessment werden zowel klinische gegevens verzameld (medicatie, etc) op basis van bevraging van de arts als ook ernst van symptomen en kwaliteit van leven op basis van vragenlijsten ter attentie van patiënten. Depressie werd gemeten op basis van 2 vragen over anhedonie en depressieve stemming (de belangrijkste items binnen de DSM-5 criteria voor depressie) uit de Brief Patient Health Questionnaire 9 (PHQ-9). Datum van overlijden van patiënten werd bij elk centra bevraagd 6 maanden na de laatste inclusie van een participant.

Studie 2: Vragenlijststudie bij artsen gebruikmakend van overlijdenscertificaten (hoofdstuk 3)

In deze studie werd een vragenlijst ingevuld over de zorg en de medische besluitvorming aan het levenseinde van overledenen. Deze vragenlijst werd opgestuurd naar de attesterende artsen van een representatieve steekproef (n = 6188) van overlijdenscertificaten in Vlaanderen. In deze vragenlijst werden ook vragen over doorverwijzing naar gespecialiseerde zorg en redenen voor niet doorverwijzing opgenomen. Deze gegevens zijn verzameld in de eerste helft van 2013. Deze methode werd voor het eerst aangewend in Nederland, het is de vierde maal dat deze methode in Vlaanderen wordt gebruikt.

Studie 3: Een gerandomiseerd gecontroleerd onderzoek naar het effect van vroege en systematische integratie van palliatieve zorg in de oncologische zorg

We hebben een gerandomiseerde gecontroleerde studie uitgevoerd om vroege en systematische integratie van palliatieve zorg te evalueren in de standaard oncologische zorg. Van april 2013 tot februari 2016 hebben we 186 patiënten met geavanceerde kanker met een levensverwachting van ongeveer 1 jaar die behandeld werden in het UZ Gent geïncludeerd. Patiënten werden gevraagd om, indien gewenst, een naaste te identificeren die ook kon deelnemen aan het onderzoek, 115 naasten gaven een akkoord voor deelname. Patiënten en hun naasten werden op willekeurige manier toegewezen aan vroege en systematische palliatieve zorg (interventiegroep) of aan standaard oncologische zorg (controlegroep). Participanten die werden toegewezen aan de interventiegroep hadden binnen 3 weken na deelname een eerste ontmoeting met een verpleegkundige van het palliatief support team. Verdere consultaties met een verpleegkundige van het palliatief support team werden maandelijks georganiseerd op een moment van een geplande raadpleging/behandeling in het ziekenhuis. In de controlegroep werd het palliatief support team enkel betrokken op doorverwijzing van de arts of vraag van de patiënt (dus niet op systematische manier), meestal laat in het ziektetraject.

Patiënten en naasten werden gevraagd om vragenlijsten in te vullen op baseline, 12 weken en vervolgens 6-maandelijks. De primaire uitkomstmaat van deze studie is kwaliteit van leven van patiënten op 12 weken, gemeten met de European Organisation for Research and Treatment of Cancer (EORTC) QLQ C30 vragenlijst. Naast dataverzameling via vragenlijsten, werden ook de medische dossiers geconsulteerd voor informatie over het behandeltraject en duur van overleving.

Belangrijkste bevindingen

De resultaten en antwoorden op de onderzoeksvragen zijn hieronder samengevat onder 3 relevante thema's van het proefschrift.

Uitdagingen bij integratie van palliatieve zorg in de oncologische zorg

Symptomen van ernstige depressie (hoofdstuk 2)

We voerden een analyse uit op een kwantitatieve vragenlijststudie bij 1699 patiënten met kanker die palliatieve zorg kregen. Patiënten werden gevraagd om maandelijks een vragenlijst in te vullen over een periode van 6 maand of tot en met overlijden. Hieruit bleek dat 52% van de patiënten met vergevorderde kanker rapporteerden dat er minstens eenmaal symptomen van ernstige depressie optraden. Het percentage van patiënten met dergelijke symptomen was het hoogst bij aanvang van de studie maar opmerkelijk was dat dit percentage zakte naarmate de tijd vorderde. We observeerden ook een grote variabiliteit in het rapporteren van symptomen van depressie binnen individuele trajecten van patiënten: 26% van de patiënten veranderden tussen aanvang van de studie en 1 maand van het ervaren van ernstige symptomen van depressie naar het niet ervaren van deze symptomen (13.8%) of vice versa (12.5%).We onderzochten ook welke factoren de grootste invloed hebben op het al dan niet ervaren van symptomen van ernstige depressie. Naast tijd, bleken ook dat hogere pijn, slechtere performance status en slechter fysiek functioneren belangrijke voorspellers waren voor het ervaren van symptomen van ernstige depressie.

Deze bevindingen tonen aan dat mensen met kanker die tevens een palliatieve zorg behandeling krijgen vaak klachten ervaren van mogelijks ernstige depressie, maar dat dit wisselend kan zijn tijdens het ziektetraject We toonden ook aan dat symptomen van ernstige depressie beïnvloedt worden door verschillende factoren, zoals pijn of fysiek functioneren. Dit alles toont het belang aan van frequente screening voor symptomen van depressie bij mensen met geavanceerde kanker.

Doorverwijzing naar gespecialiseerde palliatieve zorg (hoofdstuk 3)

Met behulp van een vragenlijststudie bij certificerende artsen onderzochten we wanneer mensen met verschillende types kanker werden doorverwezen naar gespecialiseerde palliatieve zorg en welke redenen werden aangeven om niet door te verwijzen. Uit onze resultaten blijkt dat doorverwijzing van patiënten met kanker naar gespecialiseerde palliatieve zorg reeds relatief hoog is in Vlaanderen. Wel vonden we dat

mensen met hematologische kanker een lagere kans hebben op het gebruik van palliatieve zorg (SPCS) in vergelijking met patiënten met solide kankers. Het gebruik van gespecialiseerde palliatieve zorg varieerde van 56% voor hematologische kanker tot 86% voor hoofd/hals kanker. We vonden ook evidentie van late verwijzing voor alle kankertypes, variërend van 29 dagen (borst) tot 10 dagen (hematologische) vóór de dood. Patiënten met hematologische kankers kregen ook het vaakst behandelingen die gericht waren op levensverlenging of curatie in de laatste week van het leven. Ten slotte rapporteerden artsen als belangrijkste reden om niet door te verwijzen naar palliatieve zorg dat de reguliere zorg al voldoende tegemoet kwam aan de palliatieve en ondersteunende zorgbehoeften van de patiënt of dat palliatieve zorg niet of onvoldoende zinvol was voor de patiënt.

Onze studie draagt bij tot het besef dat doorverwijzing naar gespecialiseerde palliatieve zorg voor patiënten met kanker in Vlaanderen reeds relatief hoog is, maar dat dit nog steeds (te) laat in het ziektetraject voorkomt.

Een gerandomiseerd gecontroleerd onderzoek naar vroege integratie van palliatieve zorg in de oncologie studie (Hoofdstuk 4).

Bij de start van onze studie waren dat studies naar vroege integratie van palliatieve zorg in de oncologie voornamelijk afkomstig uit de Verenigde Staten en Canada en was er dus nood was aan vergelijkbaar onderzoek in Europa. We hebben vervolgens een protocol ontwikkeld van een gerandomiseerde gecontroleerde studie die we in België wilden uitvoeren om het effect van vroege en systematische integratie van palliatieve zorg in standaard oncologische zorg te evalueren. Het doel was om 186 patiënten met vergevorderde kanker te includeren van de afdelingen Medische Oncologie, Digestieve Oncologie en Thoracale Oncologie van het Universitair Ziekenhuis Gent. Patiënten konden ook een naaste identificeren om deel te nemen aan de studie. Aan patiënten en naasten werd gevraagd om vragenlijsten in te vullen over kwaliteit van leven, gemoedstoestand, ziektebegrip en tevredenheid met de zorg[40].

Het effect van vroege en systematische integratie van palliatieve zorg in de oncologische zorg (Hoofdstuk 5-7)

Aan de hand van een gerandomiseerd gecontroleerd onderzoek hebben we onderzocht of vroege en systematische integratie van palliatieve zorg naast standaard oncologische zorg (interventiegroep), vergeleken met de standaardzorg alleen (controlegroep), een positieve invloed heeft op patiënten met gevorderde kanker met een geschatte levensverwachting van 12 maanden. De studie toont aan dat patiënten

die werden toegewezen aan de interventie groep een toename rapporteerden op hun algemene kwaliteit van leven op 12 weken(primaire uitkomstmaat) en 18 weken na baseline. Dit in vergelijking met patiënten uit de controlegroep. Vroege en systematische integratie van palliatieve zorg leidde niet tot significante verschillen in overleving, gemoedstoestand of ziektebegrip. Ook konden we geen overtuigende verschillen aantonen op symptoomlast of functioneren. Uit onze studie bleek wel dat participanten die vroege en systematische integratie van palliatieve zorg kregen, meer consultaties hadden met een psycholoog.

Het verbeteren van de kwaliteit van leven van patiënten met een levensbedreigende ziekte evenals die van hun naasten is erkend als een van de belangrijkste doelen van de palliatieve zorg. Aan de hand van een gerandomiseerd gecontroleerd onderzoek, hebben we ook het effect van vroege en systematische integratie van palliatieve zorg in de oncologie op de kwaliteit van leven van naasten van patiënten met gevorderde kanker onderzocht. Naasten die waren toegewezen aan de interventiegroep rapporteerden een verbetering in de mentale component van kwaliteit van leven na 18 weken. in vergelijking met naasten die standaard oncologische zorg kregen. Hun kwaliteit van leven (zowel de fysieke component als de mentale component) was ook significant hoger op één, drie en zes maanden voorafgaand aan het overlijden van de patiënt. Er werden geen verbeteringen gevonden tussen beide groepen in de fysieke component score (PCS) van kwaliteit van leven, gemoedstoestand, tevredenheid met zorg of ziektebegrip na 12 of 18 weken.

We onderzochten ook het effect van vroege en systematische integratie van palliatieve zorg in de oncologische zorg op de kwaliteit van leven van patiënten kort voor overlijden en op de zorg aan het levenseinde. Patiënten in de interventiegroep rapporteerden een betere kwaliteit van leven op zes, drie en een maand voorafgaand aan de dood in vergelijking met patiënten uit de controlegroep. Deze studie toonde geen verschil aan tussen beide groepen wat de zorg aan het levenseinde betreft, zoals bijv. in het voorkomen van agressieve levenseinde zorg.

Deze bevindingen van het uitgevoerde gerandomiseerde gecontroleerd onderzoek tonen aan dat vroege en systematische palliatieve zorg geïntegreerd in de oncologische zorg, in tegenstelling tot palliatieve zorg op vraag in de standaardzorg, de kwaliteit van leven van patiënten significant verbetert. Dit zowel op korte als op lange termijn. Tevens konden we aantonen dat ook de kwaliteit van leven van naasten van patiënten met gevorderde kanker significant verbetert kort na de diagnose van gevorderde ziekte en kort voor het overlijden van de patiënt. Dit effect werd gevonden door een gestructureerde palliatieve zorg interventie aan te bieden die voornamelijk op de patiënt was gericht maar de deelname van naaste stimuleerde.

Discussie en aanbevelingen

Depressie in gespecialiseerde palliatieve zorg

Een belangrijke bevinding in dit proefschrift is dat meer dan de helft van patiënten met gevorderde kanker die deelnamen aan een programma voor palliatieve zorg rapporteerde dat ze tijdens hun ziektetraject leden aan symptomen van ernstige depressie. Dit onderstreept het belang van zorgvuldig en systematische screening van symptomen zoals depressie. Dit geldt des te meer omdat recente bevindingen hebben aangetoond dat depressie een nefaste invloed heeft op kwaliteit van leven bij patiënten met gevorderde kanker. Symptomen van ernstige depressie namen af bij patiënten met kanker die reeds werden verzorgd door multidisciplinaire palliatieve zorgteams. Dit zou kunnen suggereren dat het toevoegen van een multidisciplinaire aanpak van palliatieve zorg aan reguliere oncologische zorg dergelijke symptomen vermindert vanwege de meer expliciete aandacht voor pijn- en symptoomcontrole, spirituele, psychologische en sociale behoeften. Dit komt overeen met recente gegevens dat vroege palliatieve zorg een gunstig effect heeft op de depressie van patiënten met kanker in sommige landen.

Toegang tot gespecialiseerde palliatieve zorg

Een belangrijke bevinding in dit proefschrift is het feit dat het gebruik van gespecialiseerde palliatieve zorgservices in België hoog is, maar nog steeds laat in het ziektetraject voorkomt. Dit toont aan dat de heersende visie op palliatieve zorg nog steeds een traditioneel dichotoom model van medische zorg volgt, waarbij palliatieve zorg wordt opgevat als comfortzorg en wordt aangeboden wanneer een curatieve of levensverlengende behandeling niet langer geschikt is. Hoewel patiënten met vergevorderde kanker vaak veel last hebben van ernstige symptoomlast, zijn gespecialiseerde palliatieve zorgservices niet evenwaardig toegankelijk voor al deze patiënten. Onze studie toonde namelijk aan dat patiënten met hematologische kanker minder kans hebben om te worden verwezen naar gespecialiseerde palliatieve zorg in vergelijking met patiënten met solide kanker. De voornaamste redenen bij alle kankers, opgegeven door artsen, om niet door te verwijzen was dat palliatieve zorg als niet zinvol werd ervaren of dat de standaardzorg al voldoende voldeed aan de zorgnoden van patiënten. Ook werd gemeld dat patiënten de verwijzing naar palliatieve zorg weigerden. Op basis van deze evidentie, zou men kunnen stellen dat artsen en de samenleving onvoldoende bewust zijn van wat palliatieve zorg kan bijdragen aan de zorg en dat dit een belangrijke barrière vormt voor integratie van palliatieve zorg in oncologie.

Tijdige integratie van gespecialiseerde palliatieve zorg in de oncologie

Een significant effect op de kwaliteit van leven

Vroege en systematische integratie van palliatieve zorg in de oncologie resulteerde in significante verbeteringen op de algemene kwaliteit van leven van zowel patiënten met vergevorderde kanker als hun naasten (Hoofdstuk 4-7). Dit werd waargenomen op de primaire uitkomst van het onderzoek, na 12 weken (hoofdstuk 5), maar ook later na 18 weken en kort voor de dood (hoofdstuk 7).Dit proefschrift draagt bij aan de literatuur omdat ons model (Hoofdstuk 4) werd geïmplementeerd in een omgeving waar patiënten reeds standaard psychosociale ondersteuning krijgen als onderdeel van de standaard oncologische zorg. Dit suggereert dat het aanbieden van psychosociale zorg in de oncologische zorg alleen niet voldoende is, maar dat de extra ondersteuning door een gespecialiseerd palliatieve zorgteam leidt tot verdere significante verbeteringen in de kwaliteit van leven. Een waarschijnlijk mechanisme van dit effect is het verschil in focus in de zorgverlening van het - multidisciplinaire - oncologieteam en het palliatieve zorgteam. Hoewel de focus van het oncologische team terecht meer ligt op het behandelen van de kanker, kijken gespecialiseerde palliatieve zorgteams meer naar de hele persoon en minder naar de ziekte. De palliatieve zorgverpleegkundigen in onze studie verstrekten zowel emotionele als fysieke ondersteuning, besteedden tijd aan besluitvorming en voorafgaande zorgplanning en ondersteunden niet enkel de patiënt, maar ook hun naasten. Het is mogelijk dat deze extra steun, die een extra patiëntgerichte focus toevoegt aan de oncologische zorg, een positieve invloed op de kwaliteit van leven van patiënten.

Er zijn echter verschillende andere plausibele mechanismen van het effect van vroege integratie van palliatieve zorg. De interventie van de gerandomiseerde gecontroleerde trial, beschreven in hoofdstuk 4, is een complexe interventie die bestaat uit verschillende componenten: (1) training van het palliatieve zorgteam, (2) semi-gestructureerde consultaties voornamelijk met palliatieve zorgverpleegkundigen, (3) gestructureerde symptoom assessment en (4) integratie van palliatieve zorg in de oncologie. Dit werpt de vraag op welke de kerncomponenten zijn van vroege palliatieve zorg die leiden tot de verbetering in kwaliteit van leven voor patiënten en hun naasten.

Onze studie staat ons niet toe om duidelijke conclusies te trekken, maar we zullen enkele plausibele mechanismen bespreken die van invloed zouden kunnen zijn. Wanneer we kijken naar welke onderwerpen tijdens de consulten in de eerste 18 weken werden besproken, zien we dat symptoom management(32%) en ziektebegrip (29%) het meest werden besproken. Dit zou kunnen suggereren dat het systematisch

aanpakken van symptoom management, dat ook symptoom assessment inhoudt, en ziektebegrip de belangrijkste determinanten zijn van de verbetering van de kwaliteit van leven.

Een andere potentiële belangrijke determinant kan te maken hebben met de systematische aanpak van palliatieve zorg die in dit model is opgenomen, in tegenstelling tot palliatieve zorg op vraag in de standaardzorg. In onze studie werden de consultaties met het palliatieve zorgteam op gestructureerde basis gepland en dit reeds vroeg in het ziektetraject. Dit biedt patiënten en hun naasten de mogelijkheid om een langdurige relatie met de mensen van het palliatieve zorgteam te ontwikkelen. Het is mogelijk dat het opbouwen van een vertrouwensrelatie moeilijke gesprekken over prognose of discussies over behandelopties die aansluiten bij de zorgdoelen van patiënten en hun mantelzorgers vergemakkelijken en dat dit de kwaliteit van leven van patiënten en naasten verbeterd.

Een derde plausibel mechanisme is dat patiënten de oncologie en palliatieve zorg zien als complementaire zorg en vinden dat beide bijdragen aan een alomvattende zorg. Palliatieve zorgteams hebben enerzijds de rol om patiënten en hun familie te helpen bij het beheersen van hun symptomen, psychosociale en geestelijke ondersteuning te bieden en zorgdoelen te bespreken. Oncologen, aan de andere kant, hebben de taak om zich te concentreren op de kanker behandeling, het stabiliseren van de ziekte en het verlengen van het leven. Het is mogelijk dat patiënten en hun naasten terughoudend zijn om hun bezorgdheid ten aanzien van symptomen en ziektelast te melden aan het oncologische team uit de angst dat deze behandeling zou kunnen stop gezet worden. De extra ondersteuning van een onafhankelijk team dat gespecialiseerd is in holistische en patiëntgerichte zorg kan voor patiënten een extra mogelijkheid bieden om vragen over prognose op te helderen en openlijk over hun angsten, zorgen, symptomen en behandelingswensen te kunnen vertellen.

Kunnen we spreken van integratie?

In dit proefschrift (hoofdstuk 3) hebben we vier componenten van onze interventie beschreven, waaronder ook de integratiecomponent. Dit onderdeel betekende dat het palliatieve zorgteam niet alleen semi-gestructureerde consultaties uitvoerden, maar ook (1) vergaderingen bijwoonden op oncologische afdelingen (2) rapporteerden in elektronische patiëntendossiers en (3) persoonlijk contact opnamen met de leden van het oncologie-team om specifieke behoeften te bespreken van patiënten wanneer dat nodig werd geacht. In de literatuur was er enige kritiek op deze component van onze interventie. Er werd beargumenteerd, gebaseerd op een definitie van integratie door Leutz, dat onze interventie het meest past bij het laagste niveau van integratie dat wordt omschreven als 'verbinding'. Verbinding als concept van

integratie houdt in dat er beide teams op de hoogte zijn van de vaardigheden van de verschillende professionals. Dit betekent ook dat patiënten worden verzorgd op een geplande manier, op basis van inzicht in specifieke behoeften, maar dat het werk tussen beide teams parallel of in serie wordt uitgevoerd. Wij zijn er echter van overtuigd dat onze interventie meer heeft bereikt dan teams die parallel werken. We zien ons model liever als een "comanagement-model". Comanagement beschrijft de nauwe klinische samenwerking tussen het palliatieve zorgteam en de behandelend arts bij de patiëntenzorg in de ziekenhuisomgeving. Hoewel elk lid input levert bij het beheer van verschillende aspecten van de behandeling, ligt de algehele verantwoordelijkheid bij de behandelend arts. Het feit dat ons model meer is dan alleen een verbinding, komt ook tot uiting in de toename van het aantal raadplegingen door de psychologen van het oncologie-team. Wij zijn het echter met de auteurs eens dat er ruimte is voor verbetering in ons model met betrekking tot integratie.

Dit proefschrift laat ook zien (Hoofdstuk 6) dat de introductie van palliatieve zorg kort na de diagnose van kanker leidt tot significante verbeteringen in de kwaliteit van leven van naasten vergeleken met de standaardzorg. Deze effecten werden zichtbaar later in het ziektetraject van patiënten. Belangrijk om op te merken is dat dit model van vroege palliatieve zorg voornamelijk gericht is op patiënten met kanker en minder rechtstreeks op de naasten. Dit komt overeen met de literatuur, veel interventies met positieve resultaten voor naasten van patiënten met kanker zijn voornamelijk bedoeld om de zorg gericht aan de patiënt aan te pakken, het welzijn van naasten is vaak een secundaire focus. Het is mogelijk dat interventies die evenveel aandacht besteden aan de behoeften van kankerpatiënten als aan die van naasten zouden kunnen leiden tot betere gezondheidsvoordelen voor naasten[64]

Aanbevelingen voor onderzoek, beleid en praktijk

Onze bevindingen suggereren dat er ruimte is voor verbetering in het moment van doorverwijzing van gespecialiseerde palliatieve zorg voor patiënten met gevorderde kanker. Op basis van de studies in dit proefschrift geven we enkele belangrijke aanbevelingen voor onderzoekers, clinici en beleidsmakers met betrekking tot het initiëren en leveren van gespecialiseerde palliatieve zorg in de oncologie.

Implicaties voor onderzoek

Er kunnen verschillende aanbevelingen voor toekomstig onderzoek worden gedaan en enkele daarvan worden hieronder beschreven.

Het initiëren van palliatieve zorg vlak na de diagnose voor patiënten met vergevorderde kanker verbetert de kwaliteit van leven van patiënten die behandeld worden in het ziekenhuis. Er is echter verder onderzoek nodig om de mechanismen te verduidelijken van welke componenten van de palliatieve zorg interventies tot deze effecten leiden. Hieromtrent heersen er nog vele vragen: wat is de optimale inhoud van vroege palliatieve zorg? Zijn modellen met minder frequente consultaties even gunstig voor patiënten? Wat is het ideale niveau van integratie? Hoe verschilt palliatieve zorg die vroeg in het ziektetraject wordt aangeboden van palliatieve zorg die laat in het ziektetraject wordt aangeboden? We observeerden ook een hoge prevalentie van symptomen van depressie in de palliatieve zorg voor mensen met vergevorderde kanker. Zou palliatieve zorg die geboden wordt door een interdisciplinair team, met psychologen en psychiaters die ondersteuning bieden bij psychologische assessment en ondersteuning, de kwaliteit van leven van patiënten verder verbeteren en symptoomlast verder verminderen? Deze vragen kunnen worden beantwoord met zowel kwalitatieve als kwantitatieve onderzoeksmethoden.

Dit proefschrift laat ook zien dat patiënten met hematologische kanker minder kans hebben om doorverwezen te worden naar gespecialiseerde palliatieve zorgservices en dat wanneer er doorverwezen wordt, dit pas laat gebeurt in het ziektetraject. Wel is het geweten dat patiënten met hematologische kanker ook een aanzienlijke ziektelast ervaren en vaak een slechte kwaliteit van leven hebben. Hoewel werd aangetoond dat vroege palliatieve zorg gunstig is voor patiënten met gevorderde solide kankers, is het effect bij patiënten met hematologische kanker nog steeds onbekend aangezien de meeste klinische trials rond vroege palliatieve zorg deze patiëntenpopulatie niet omvatten. Er zijn robuuste studies nodig van vroege palliatieve zorg in deze patiëntenpopulatie.

Implicaties voor de praktijk

Op basis van de bevindingen van dit proefschrift kunnen aanbevelingen worden gedaan om de integratie van gespecialiseerde palliatieve zorg in de oncologie te verbeteren. Onze aanbevelingen zijn specifiek gericht op oncologen en het gespecialiseerd palliatieve zorgteam werkzaam in het ziekenhuis. Deze aanbevelingen hebben voornamelijk betrekking op volwassenen (leeftijd 18 jaar en ouder) met vergevorderde kanker. Natuurlijk kan palliatieve zorg ook worden geleverd aan andere patiëntengroepen en door hulpverleners die niet gespecialiseerd zijn in palliatieve zorg maar dergelijke aanbevelingen vallen buiten het bestek van dit proefschrift.

Hieronder bespreken we enkele aanbevelingen voor vroege en systematische integratie van palliatieve zorg in de oncologische zorg:

- Oncologen en specialisten in palliatieve zorg zouden samen richtlijnen moeten ontwikkelen over doorverwijzing naar gespecialiseerde palliatieve zorg van patiënten met kanker. De meeste onderzoeken naar vroege integratie van palliatieve zorg gebruikten prognose als criterium voor doorverwijzing. In dit proefschrift kwamen mensen vergevorderde kanker met een levensverwachting van ongeveer 12 maanden (beoordeeld door de behandelende oncoloog) in aanmerking voor vroege integratie van palliatieve zorg in de oncologische zorg. Wij zijn van mening dat gestandaardiseerde verwijzingscriteria een aanvulling kunnen bieden op dit klinisch oordeel om een passende verwijzing mogelijk te maken. Deze verwijzingscriteria moeten echter ook worden afgestemd op de middelen die beschikbaar zijn in de verschillende instellingen.

- Gestructureerd consultaties met het palliatieve zorgteam: de literatuur toont de voordelen aan van vroege palliatieve zorg voor patiënten met vergevorderde kanker die op een gestructureerde manier wordt aangeboden in tegenstelling tot palliatieve zorg op vraag. We raden dan ook aan om consultaties op een gestructureerde manier, bijvoorbeeld maandelijks, aan te bieden.

- Aandacht voor naasten: er bestaat algemene consensus in de literatuur dat het welbevinden van patiënten en naasten gelinkt zijn aan elkaar wanneer ze geconfronteerd worden met een levensbedreigende aandoening. Beiden hebben dan ook behoefte hebben aan ondersteuning door hulpverleners. Clinici moeten zich ervan bewust zijn dat naasten ook positieve effecten kunnen ervaren van vroege en systematische integratie van palliatieve zorg in de oncologische zorg en dat holistische zorg zich best richt op de patiënt als ook de naaste.

- Integratie van palliatieve zorgteam: we toonden een voordeel aan op de kwaliteit van leven van patiënten en naasten op basis van een model van palliatieve zorg waarbij leden van het palliatieve zorgenteam aanwezig waren tijdens multidisciplinaire overlegmomenten. Wij raadden aan dat een hulpverleners van het palliatieve zorgteam deelnemen aan multidisciplinaire overlegmomenten van oncologische teams.

Implicaties voor beleid

We hebben aangetoond dat vroege palliatieve zorg een positieve invloed heeft op patiënten met vergevorderde kanker en hun naasten en onderstrepen daarom moet het belang van tijdige integratie van gespecialiseerde palliatieve zorg in de oncologische zorg. Deze aanbevelingen voor de praktijk kunnen het best worden bereikt als ze samengaan met enkele veranderingen op beleidsniveau.

We vatten deze hieronder kort samen:

1) De resultaten van dit proefschrift tonen het belang aan van sensibilisering van professionele hulpverleners, patiënten en de bredere bevolking met betrekking tot wat palliatieve zorg inhoudt en kan betekenen.
2) Er zou een trainingsprogramma moeten aangeboden worden voor hulpverleners in de palliatieve zorg die hen nieuwe vaardigheden aanleert die nodig zijn voor het implementeren van vroege palliatieve zorg.
3) Palliatieve zorg is het afgelopen decennium een van de snelst groeiende specialismen in de geneeskunde[51] en onze aanbeveling om palliatieve zorg vroeg en systematisch te integreren in de oncologische zorg, draagt bij aan de toenemende vraag. Hoewel gespecialiseerde palliatieve zorg relatief goed beschikbaar is in België, is er een nood aan voldoende middelen en infrastructuur om dit palliatief zorgmodel te kunnen implementeren in de dagelijkse klinische praktijk.

Curriculum vitae and list of publications of Gaëlle Vanbutsele

Curriculum vitae

Gaëlle Vanbutsele, born April 9, 1985 (Ronse, Belgium) obtained her Master's degree in clinical psychology in 2009 (Ugent) and obtained a Master's degree in business management (Hogeschool-Universiteit Brussel) in 2010. After that, she worked as an onco-psychologist at AZ Sint Maria in Halle. Since 2012, she is associated as a researcher at the End-Of-Life Care Research Group of the Ghent Univeristy & the Vrije Universiteit Brussel.

She and Christophe Balcaen have two fantastic children, Hector and Edgar.

List of publications

Articles in international peer-reviewed journals.

Vanbutsele G, Pardon K, Van Belle S, Surmont S, De Laat M, Colman R, Eecloo K, Cocquyt V, Geboes K, Deliens L. Effect of early and systematic integration of palliative care in patients with advanced cancer: A randomised controlled trial. Lancet Oncol 2018 Mar; 19(3): 394–404. [2017 Impact Factor: 36.418, Journal ranking Q1,D1]

Vanbutsele G, Van Belle S, De Laat M, Surmont V, Geboes K, Eecloo K, Pardon K*, Deliens L*. The systematic early integration of palliative care into multidisciplinary oncology care in the hospital setting (IPAC), a randomized controlled trial: The study protocol. BMC Health Serv Res 2015 Dec 15; 15:554. [2017 Impact Factor: 1.843, 2015 Impact Factor: 1.606, Journal ranking Q3

Vanbutsele G, Deliens L, Cocquyt V, Cohen J, Pardon K*, Chambaere K*. Use and timing of referral to specialized palliative care services for people with cancer: a mortality follow-back study among treating physicians. (Submitted)

Vanbutsele G , Pardon K, De Laat M, Jacobs C, Colman R, Loge JH , Hjermstad MJ , Kaasa S, Deliens L. Prevalence and variability of a positive screening for major depression in palliative care cancer patients. The longitudinal European Palliative Care Cancer Symptom study (EPCCS-study).

Vanbutsele G, Van Belle S, Surmont S, De Laat V, Colman R, Eecloo K, Naert E, Geboes K, Deliens L*, Pardon, K*. Early and systematic integration of palliative care in oncology: the effect on informal caregivers.(Submitted)

Vanbutsele G, Van Belle S, Surmont V, De Laat M, Colman R, Eecloo K, Naert E, De Man M., Geboes K Deliens L*, Pardon K*. The effect of early and systematic integration of palliative care at the end-of-life of cancer patients: a randomized controlled trial. (Submitted)

Other publications and chapters in books

Vanbutsele G, Pardon K, Van Belle S, Surmont S, De Laat M, Colman R, Eecloo K, Cocquyt V, Geboes K, Deliens L. Effect of early palliative care : complex intervention and complex results: Author's reply. Lancet Oncol 2018; 19: e222. 2017 [Impact Factor: 36.418, Journal ranking Q1,D1]

Pardon K, **Vanbutsele G**. Palliative Care and Cancer. In: MacLeod, R. & Van den Block, L. eds. In: Textbook of Palliative Care. Cham: Springer, 2018.

Oral presentations given at international conferences and seminars

Tijdige integratie van palliatieve zorg bij mensen met kanker in het ziekenhuis. Presentation given at the Integrate congres. Tijdige integratie van palliatieve zorg bij mensen met kanker en COPD. Ghent (Belgium). November 2017.

The effect of systematic early integration of palliative care into multidisciplinary oncology care in the hospital setting (IPAC), a randomized controlled trial. Presentation given at 10th World Research Congres of the European Association for Palliative care, Bern (Switzerland). May 2018.

Early and systematic integration of palliative care in multidisciplinary oncology care: the effect on informal caregivers. Presentation given at 10th World Research Congres of the European Association for Palliative care, Bern (Switzerland). May 2018.

Prevalence of a positive screening in advanced cancer patients in a palliative care setting. Presentation given at the public seminar "Psychological Suffering" organized by the End-of Life Care Research Group, Brussels (Belgium), December 2017.

The effect of systematic early integration of palliative care into multidisciplinary oncology care in the hospital setting (IPAC), a randomized controlled trial. Presentation given at 7th International Seminar of the European Palliative Care Research Centre and European Association for Palliative Care Research Network, Oslo (Norway), October 2017.

Referral and integration of specialised palliative care in cancer. Presentation given at Public Seminar "Palliative care in cancer" organized by the End-of Life Care Research Group, Brussels (Belgium). October 2016.

The systematic early integration of palliative care into multidisciplinary oncology care in the hospital setting (IPAC), a randomized controlled trial. Presentation given at the Pre-congress of 9th World Research Congress of the European Association for Palliative Care, Dublin, (Ireland). May 2016.

Early Palliative Care in Oncology Care. Presentation given at Seminar on Palliative Care in Oncology at the Department of Respiratory Medicine, University Hospital Ghent, Ghent (Belgium). May 2016.

Geplande en systematische palliatieve zorg vroeg in het ziektetraject van de oncologische patiënt. Presentation given at the FLIECE Congres- Palliatieve zorg in het ziekenhuis, Ghent (Belgium). December 2013.