Dissertation submitted in fulfilment of the requirements
for the award of the degree of Doctor (PhD) in Social Health Sciences

END-OF-LIFE CARE IN ADVANCED CANCER

AN INTERNATIONAL CHALLENGE

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January 2022

Vrije Universiteit Brussel
Faculty of Medicine and Pharmacy
Department of Family Medicine and Chronic Care
Academic year 2021-2022

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Printing
Uitgeverij VUBPRESS Brussels University Press
VUBPRESS is an imprint of ASP nv
(Academic and Scientific Publishers)
Keizerslaan 34
1000 Brussels
Tel. +32 (0)2 289 26 56
E-mail: info@aspeditions.be
www.vubpress.be

ISBN 9789461172914
NUR NOG AAN TE VULLEN
Legal deposit D/2022/11.161/006

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2021-2022

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“Mijn leven is kort geweest
maar wel heel gelukkig.”

Theo Broekmans

* 25 oktober 1985
† 19 november 2000

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Chapter 3:
Verkissen MN, Hjermstad MJ, Van Belle S, Kaasa S, Deliens L, Pardon K. Quality of life and symptom intensity over time in people with cancer receiving palliative care: results from the international European Palliative Care Cancer Symptom study. *PLoS ONE*, 2019; **14**(10): e0222988. [2019 SCI impact factor 2.740; journal ranking Q2; ranking n° 27 of 71 in MULTIDISCIPLINARY SCIENCES]

Chapter 4:
Verkissen MN, Penders YWH, Onwuteaka-Philipsen BD, Moreels S, Donker GA, Vega Alonso T, Van den Block, Deliens L. End-of-life communication in advanced cancer: international trends (2009-2014). *BMJ Supportive & Palliative Care*, 2020; Published online ahead of print of print, 2020 Apr 27. [2020 SCI impact factor 3.568; journal ranking Q2; ranking n° 35 of 107 in HEALTH CARE SCIENCES & SERVICES]

Chapter 5:
Verkissen MN, Leemans K, Van den Block L, Deliens L, Cohen J. Information provision as evaluated by people with cancer and bereaved relatives: a cross-sectional survey of 34 specialist palliative care teams. *Patient Education and Counseling,* 2019; **102**(4): 768-75. [2019 SCI impact factor 2.607; journal ranking Q1; ranking n° 16 of 108 in SOCIAL SCIENCES, INTERDISCIPLINARY]

Chapter 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. *British Journal of Cancer*, 2018; **118**(10): 1369-76. [2018 SCI impact factor 5.416; journal ranking Q1; ranking n° 44 of 230 in ONCOLOGY]

D

Dankwoord | Acknowledgements

DANKWOORD | ACKNOWLEDGEMENTS

Be like a snail: slow but sure.

Dat leken me wijze woorden om dit dankwoord mee te starten. ‘Hoe gaat het met het proefschrift?’ In de afgelopen jaren moeten er minstens honderden gesprekken begonnen zijn met deze vraag. Ik bewonder de vasthoudendheid, want ik moest het antwoord op deze vraag meestal schuldig blijven. Met het schrijven van dit stuk leg ik dan toch echt de laatste hand aan het beruchte boekje. Dat betekent dat de afsluiting van een bijzondere periode uit mijn leven dichtbij is. Het was een weg van lange adem, die veel dichter bij mijzelf kwam dan ik vooraf had kunnen bedenken. Gelukkig stond ik er nooit helemaal alleen voor. Onderzoek doen is een gezamenlijke inspanning. Het is daarom tijd om stil te staan bij een aantal mensen die ik dankbaar ben voor hun inbreng, adviezen en ondersteuning gedurende mijn traject, ieder op zijn of haar eigen manier.

Beste **Luc**, jouw expertise in palliatieve zorgonderzoek, kritische blik en scherpe inzichten hebben een meerwaarde betekend voor mijn werk. Als promotor heb je de nodige knopen doorgehakt. Bedankt dat je me de kans hebt gegeven om deel uit te maken van een gedreven onderzoeksgroep, en om ervaring op te doen binnen de kaders van een uniek internationaal project. Ik wil mijn kans ook nog grijpen om mijn excuses aan te bieden voor de keren dat ik zonder het zelf in de gaten te hebben ongepaste taal gebruikt heb omdat ik de woorden *bureau* en *kamer* weer eens door elkaar haalde (deze excuses gelden ook voor anderen die dit lezen, want het kwam in menig eerder dankwoord al eens voorbij…).

Beste **Aline**, in een laat stadium van mijn doctoraat werd je opeens met mij opgezadeld, precies op een moment dat er voor mij veel onzekerheid, en daardoor voor jou waarschijnlijk veel onduidelijkheid was. Ik kan me dan ook voorstellen dat deze begeleidingstaak niet altijd even vanzelfsprekend voor je is geweest. Een zekere flexibiliteit ten aanzien van afspraken en deadlines vanuit jou was steeds nodig. Ik wil je bedanken dat je de begeleiding toch aan bent gegaan en het geduld hebt gehad om deze voort te zetten, ook toen het allemaal langer bleek te duren.

Beste **Dirk**, hopelijk gaat het goed, of toch minimaal ‘ça va!’ met je. Het is inmiddels alweer even geleden, maar we werkten een periode intensief samen. Je hebt me destijds door de eerste hectische periode van het ACTION-project heen geloodst. Goede herinneringen heb ik aan de tripjes naar Rotterdam, met name aan de terugreizen die vaak garant stonden voor een ontspannen half uurtje ‘pintelieren’ in de Thalys-bar na het werk. Dank voor het vertrouwen dat je altijd in mijn werk had. *Festina lente*, ‘haast u langzaam’, één van je meest befaamde zegswijzen ben ik niet vergeten. Sterker nog: ik heb deze levenswijsheid misschien wel iets te letterlijk genomen…

Beste leden van de doctoraatsjury, **Dirk Devroey**, **Nele Adriaenssens**, **Kim Beernaert**, **Lore Decoster**, **Sebastiaan Engelborghs**, **Lore Lapeire** en **Roeline Pasman**, ik wil jullie zeer hartelijk danken voor de tijd die jullie hebben willen vrijmaken om mijn werk kritisch te lezen en te beoordelen.

Dear members of the **ACTION consortium**, thank you all for giving me the opportunity to work and collaborate with so many great people, to learn from your expertise and to be part of such a supportive team throughout all these years. Special thanks to my ACTION buddies **Lea**, **Marieke**, **Caroline** and **Francesco**! We've had some great times together.

Team Rotterdam: **Agnes**, **Ida**, **Judith**, **Lea**, als ACTION-coördinator waren jullie verantwoordelijk voor het in goede banen leiden van deze ambitieuze studie. Ik wil jullie bedanken voor de samenwerking en voor het tot een succesvol einde brengen van het project. Ik heb hier met interesse en toewijding aan meegewerkt en ontzettend veel geleerd. De werkzaamheden voor ACTION hebben me doen inzien wat er allemaal bij een onderzoek op zo'n grote schaal komt kijken. Echt. Heel. Veel.

Kim E., je bent een grote hulp voor mij geweest bij ACTION! Je stond er misschien niet altijd om te springen om bepaalde taken over te nemen, maar je hebt je ingezet voor de studie op allerlei verschillende manieren en ik ben je heel dankbaar, dit gaf mij ruimte om te schrijven. Zonder jou was ik nu mogelijk nog met m'n eerste paper bezig.

To all **co-authors** of the various publications have I worked on during my PhD, including ACTION, EPCCS, EURO SENTIMELC, QPAC and ELD. There are too many of you to thank personally. I am grateful for everything you have done to give us the best chance of creating successful articles. Your commitment and input have been very helpful, and I appreciate the effort and time you took of your busy schedules to comment on my work.

Evelien en **Mariska**, dankjewel voor het ontwerp van de originele, persoonlijke cover en het opmaken van het binnenwerk van het boekje. Het was een fijne samenwerking!

Lieve **collega's van het levenseinde**, mogelijk ga ik het nu tot in de eeuwigheid verpesten bij een paar van jullie, maar ik vrees dat ik niet iedereen kan benoemen omdat dit dankwoord (nu al) veel te lang wordt met alle samenwerkingen en de vele verschillende bureaus (of waren het toch *kamers*) die dit ZrL-fossiel in de loop van de jaren is afgegaan. Oké, ik stop al, want dit begint steeds dubieuzer te klinken…

Nadine en **Geertje**, de hele onderzoeksgroep zou verloren zijn zonder jullie. Ik kan alleen maar heel veel respect en waardering hebben voor het werk wat jullie iedere dag doen.

Kim E., **Gaëlle**, **Naomi** (en **Laure**, die regelmatig even kwam buurten), hoe gezellig was het om het K1-psychologen-bureau met jullie te delen? Ik denk dat het alleen al onze gemeenschappelijke liefdes (katten, foute-Facebook-GIF'jes) waren waardoor onze chakra's meteen verbonden werden. Geen idee wat chakra's precies zijn trouwens.

Over chakra's gesproken, dit doet me meteen aan ons Isabelleke denken. (Ik zou niet weten waarom...) **Isabel**, ik heb jou de laatste jaren, maar vooral maanden, steeds beter leren kennen, en je bent echt een schatje. Bedankt voor alles. Ik heb al zin in ons wellness-en-wijntjes-weekendje!

Dan nog de twee collega's die er lang geleden al heel snel voor zorgden dat ik me thuis voelde in Jette.

Lenzo, bedankt voor de fijne tijden, je steun, alle lol en de eindeloze koffievoorziening. Zolang mijn 'tas' maar continu bijgevuld werd zonder dat ik zelf überhaupt iets doorhad was het leven goed. Het aroma van zwarte koffie met een werkelijk fenomenale strafheid kwam ons altijd al vanaf de andere kant van de gang tegenmoet. Wat wil een mens nog meer? (Met nadruk op mens, want of de kamerplanten die ook royaal voorzien werden er ook zo over dachten...) Je zou er bijna vóór 10.00 uur voor naar het werk komen. Bijna. Het had niet veel gescheeld.

Yolanda, jij bent gewoon een held. Als het aan mij lag kreeg je minimaal een standbeeld. Het afgelopen jaar dreigde ik meermaals hopeloos ten onder te gaan in een levensgevaarlijk moeras genaamd De Discussie. Steeds als ik dacht te gaan sterven, wist jij me weer te redden. Je bent er zoveel voor mij geweest tijdens de afronding van dit doctoraat, waar heb ik dat aan verdiend?

Zoë, **David**, ook jullie hebben recht op een vermelding, al is het een tijd geleden dat we elkaar zagen. We hebben elkaar enkele jaren terug in heftige omstandigheden leren kennen. Des te bijzonderder was de vriendschap die hier toen uit ontstond. Jullie zijn warme mensen die hun deur altijd hebben openstaan. Het samen paardrijden bood in die tijd troost en afleiding, daarnaast was het ook gewoon fijn om deze oude maar geliefde hobby van mij weer op te kunnen pakken (terug te zien op de cover van dit boekje). Ik wens jullie veel geluk met jullie mooie gezin.

Mijn 'Hollandse' vrienden, zoals men hier zou zeggen... bedankt! Ook nu kan ik niet iedereen opnoemen, dus ik beperk me tot diegenen die het meest betrokken zijn geweest bij mijn leven in de afgelopen jaren, in de hoop dat ik niemand vergeet. Door de afstand soms voor een wat langere periode uit het oog, niet uit het hart. De Tilburgse psychologie-matties: **Esther**, **Reiny**, **Kim**, **Meike, Juliëtte**. Ik heb het altijd erg naar m'n zin tijdens onze reünietjes. Daarnaast **Bas**, **Eva**, **Sofie** (de enige niet-Hollander uit het rijtje), **Jaimy**, **Rochelle**. Jullie hebben ieder op eigen wijze van alles betekend de voorbije periode (lees: vooral naar mijn gezeur geluisterd). Binnenkort zijn we weer landgenoten! Als dat vervelende virus ons eindelijk eens met rust laat, is het sowieso tijd voor een paar dikke *fissa's*.

Lieve **familie**, bedankt voor jullie steun in de vorm van mooie, lieve en grappige kaartjes, berichtjes, een festivalletje hier en daar, en andere kleine maar grote dingen zoals een onverwacht maar zeer ontroerend telefoontje. Dit heeft me veel goed gedaan.

Olga, allerliefste Schwess, ik ben dankbaar dat wij zussen zijn. Onze band is de laatste jaren alleen maar sterker geworden. Ik ben trots op de persoon die jij geworden bent, op veel gebieden kan ik van jou leren. Je verdient het allerbeste. Met **Sander** lijk je gelukkig al een schot in de roos te pakken te hebben (hoewel het schot bij de Delirium-tent op de Gentse Feesten niet bepaald in de roos terecht kwam...). Ik heb er een geweldige schoonbroer bij! Leuk stel zijn jullie. Ik geniet van onze weekendjes en feestjes samen, of dit nu in Nederland of in Gent is, altijd geslaagd. Ondanks de afstand zijn jullie er altijd voor mij geweest op fijne maar zeker ook op mindere momenten, er is een hoop gelachen en soms ook gehuild; weet dat ik er andersom ook voor jullie zal zijn. Ik wens jullie alle geluk van de wereld en de mooiste toekomst, op welke manier dan ook.

Pap, **mam**, lieve ouders, hoe moet ik jullie bedanken? Dankzij jullie onvoorwaardelijke steun, liefde en inspanningen heb ik kunnen komen waar ik nu dan toch lijk te zijn beland. Ik besef goed dat deze jaren ook niet altijd makkelijk voor jullie zijn geweest. Toch hebben jullie me altijd het idee gegeven dat jullie erop vertrouwden dat het op de één of andere manier allemaal wel goed zou komen. En jullie hebben ook zoveel gedaan, van het verhelpen van SPSS-syntax en Word-fiasco's tot koken, poetsen, jullie bezoekjes in Gent, de etentjes, telefoontjes, kattenfoto's, het is allemaal evenveel waard. Ik hoop dat we met ons gezin nog vele mooie momenten met elkaar mogen beleven en herinneringen mogen maken, in Roermond, in Venlo, in Eindhoven, op Tenerife – waar dan ook.

Tot slot, je bent een crazy cat lady of je bent het niet. Een bedankje aan **Pippa**, de fur baby in huis, kan niet ontbreken. Hoi Pip, je was, en bent de liefste en leukste huisgenoot. Ook al is slapen en eten het enige wat je doet, je hebt het zelfs tot een plekje op de cover van dit doctoraat geschopt. Niets zo mindful als een kat die op de thuiswerkdagen tevreden naast je toetsenbord ligt te ronken.

Mariëtte, januari 2022

A

List of abbreviations

LIST OF ABBREVIATIONS

Abbreviation	Explanation
AAHMP	American Academy of Hospice and Palliative Medicine
AIC	Akaike's Information Criterion
ACP	Advance care planning
ACTION	Advance Care Planning: an Innovative Palliative Care Intervention (study)
ANOVA	Analysis of variance
ASCO	American Society of Clinical Oncology
BE	Belgium
CI	Confidence interval
EAPC	European Association for Palliative Care
EER	Experiment-wise error rate
EF	Emotional functioning
ES	Spain
ELD	End-of-life decision
EOCD	Economic Cooperation and Development
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EPCCS	European Palliative Care Symptom (study)
ESMO	European Society for Medical Oncology
EURO SENTIMELC	European Sentinel Network Monitoring End-of-Life Care (study)
FACH	Flemish Agency for Care and Health
GP	General practitioner
HCP-CRF	Health Care Provider – Case Report Form
HCT	Multidisciplinary palliative homecare team
ICD-10	International Classification of Diseases 10th Edition
IOM	Institute of Medicine
LEIF	Life End Information Forum
NHS	National Health Service
NL	The Netherlands
OR	Odds ratio
Patient-CRF	Patient – Case Report Form
PCSs	Specialist palliative care services
PCU	Hospital-based palliative care unit
PF	Physical functioning

PRO	Patient-reported outcome
PROM	Patient-reported outcome measure
ePROM	Electronic patient-reported outcome measure
PST	Hospital-based mobile palliative support team
QPAC	Quality Indicators for Palliative Care (study)
QoL	Quality of life
SD	Standard deviation
UK	United Kingdom
WHO	World Health Organization

1

General introduction

Some parts of this general introduction are based on, or to a certain degree copied from the following articles:

Verkissen MN, De Vleminck A, Groenvold M, Jabbarian LJ, Bulli F, Cools W, Van Delden JJM, Lunder U, Miccinesi G, Payne SA, Pollock K, Rietjens JAC, Deliens L. Functional impairment, symptom severity and overall quality of life in patients with advanced lung or colorectal cancer in six European countries: baseline findings from the ACTION study. *Supportive Care in Cancer*, 2021; **29**(10):5797-810. [2020 SCI impact factor 3.603; journal ranking Q1; ranking n°9 of 68 in REHABILITATION in SCIE edition]

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Verkissen MN, Penders YWH, Onwuteaka-Philipsen BD, Moreels S, Donker GA, Vega Alonso T, Van den Block, Deliens L. End-of-life communication in advanced cancer: international trends (2009-2014). *BMJ Supportive & Palliative Care*, 2020; Published online ahead of print of print, 2020 Apr 27. [2020 SCI impact factor 3.568; journal ranking Q2; ranking n° 35 of 107 in HEALTH CARE SCIENCES & SERVICES]

Verkissen MN, Leemans K, Van den Block L, Deliens L, Cohen J. Information provision as evaluated by people with cancer and bereaved relatives: a cross-sectional survey of 34 specialist palliative care teams. *Patient Education and Counseling*, 2019; **102**(4): 768-75. [2019 SCI impact factor 2.607; journal ranking Q1; ranking n° 16 of 108 in SOCIAL SCIENCES, INTERDISCIPLINARY]

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. *British Journal of Cancer*, 2018; **118**(10): 1369-76. [2018 SCI impact factor 5.416; journal ranking Q1; ranking n° 44 of 230 in ONCOLOGY]

GENERAL INTRODUCTION

The following paragraphs will provide some background and guide the reader to the aims of this dissertation. In a subsequent part the research questions are given, the methodology, study design and setting are described, and the outline of this dissertation is listed.

1.1 BACKGROUND

1.1.1 Changes in patterns of death and dying

Death is an unavoidable part of the cycle of life. Yet the experience of dying and the way in which people deal with death and dying have not always been the same.[1] A century ago, death often came abruptly and primarily as a result of infection, accidents or childbirth complications.[2] Improved public health, medical knowledge and technology have translated into an 'epidemiological transition' characterized by an increasing life expectancy, a growing population of elderly and a fundamental change in the most commonly reported causes of death, particularly in Western high-income countries.[3,4] Societies have to deal with an ageing population and currently have the highest level of older adults in all of human history. The number of people aged 65 years or older is expected to double, from 703 million persons in 2019 to 1.5 billion in 2050 worldwide. The global share of the population aged 65 years or older climbed from 6% in 1990 to 9% in 2019, and is projected to reach 16% by 2050.[5] Over the course of the past century, mortality rates from acute causes declined and have been gradually replaced by a rising number of deaths attributable to 'non-communicable' diseases, which are now responsible for the majority (more than 73%) of global deaths.[6] These diseases tend to have more prolonged illness trajectories, with a functional decline over months or years. Examples are cardiovascular disease, the number one cause of death worldwide taking an estimated 17.9 million lives each year,[7] and cancer, the second largest cause of death globally, accounting for an estimated 9.6 million deaths each year.[8]

1.1.2 Changes in perspectives on the care for dying people

Caring for dying and incurably ill people is not a new phenomenon. However, palliative care has only received special attention in health care relatively recently. The start of the modern-day hospice movement, which developed in the United Kingdom (UK) in the mid-1960s, was an important marking point in this regard.[9] A key founder of this movement was the nurse and physician Dame Cicely Saunders (1918-2005), whose work has contributed largely to the recognition of a new specialty, palliative medicine. She introduced the concept of 'total pain', the suffering that involves all of someone's physical, psychological, social, spiritual and practical struggles,[10,11] and argued that an interdisciplinary approach to care was required to relieve the total pain of a dying person.[12] Under her guidance, the first modern hospice opened in London (St. Christopher's Hospice, 1967), where people in the terminal stage of their illness could receive multidisciplinary care according to their specific needs, after active treatment had been given up. St. Christopher's Hospice has inspired generations of practitioners and affected the expansion of hospices on a national and international scale.[13] The modern hospice approach has spread all over the world and has laid the groundwork for and further developed into the contemporary concept of palliative care.[14,15]

As the field of palliative care was quickly evolving since the late 1960s, it began to include holistic principles in the care of individuals earlier in the disease progression and in various settings, such as in hospitals and in the community.[13,16] In the 1970s palliative care came to be synonymous with the physical, psychosocial and spiritual support of patients with life-limiting illness, provided by a multidisciplinary team.[16] Although palliative care was concentrated initially on patients dying from cancer, the patient population receiving palliative care has become more diverse over time. Most people nowadays can anticipate dying at an older age from consequences of an illness with which they have lived for months or even several years.[17] Palliative care focuses on maintaining comfort and quality of life for those facing multiple, complex problems over longer periods of time. It supports in preserving a sense of dignity and control over one's life circumstances, especially (but not exclusively) in the later stages of a disabling, progressive illness.[1,18]

1.2 PALLIATIVE CARE AND END-OF-LIFE CARE IN PEOPLE WITH ADVANCED CANCER

1.2.1 Growing population of people with advanced cancer

Cancer incidence and mortality are rapidly growing across the world. The reasons for this are manifold and include not only population growth and ageing, but also a changing prevalence and distribution of certain cancer risk factors, several of which are related to socioeconomic development (e.g., diet and physical inactivity).[4,19,20] According to the World Health Organization (WHO) in its 2020 WHO Report on Cancer, one in six deaths worldwide is due to cancer.[21] In 2018, the latest year for which data is available, the global cancer burden is estimated to have increased to 18.1 million new cases and 9.6 million deaths. Europe represents just 9% of the world population, but constitutes almost a quarter (23.4%) of the total number of global cases and about a fifth (20.3%) of cancer-related mortality.[19]

Although advanced cancer usually cannot be cured, treatments may help slow the progression and extend people's lives. The rising cancer incidence and prolonged survival of patients with advanced-stage illness place increasing pressure on populations and healthcare systems across the globe, and go along with a growing critical public health need for high-quality palliative care and end-of-life care services.[22,23]

1.2.2 Palliative care

People who suffer from a serious illness such as advanced cancer live longer today than they would have only a few decades ago. Many of them experience a slow but steady progression of the disease, and the time before death is typically characterized by extended periods of disability with a higher prevalence of burdening symptoms, physical or non-physical (psychosocial, spiritual).[1,24] In order to prevent these symptoms from becoming unmanageable, the majority of people affected by long-term, progressive disease need timely and ongoing care consistent with their level of need.

Palliative care starts from the understanding that every patient has his or her own story, relationships and culture, and that he/she deserves respect as a unique individual. This respect includes providing the best available medical care, so that people can live their lives as fully and comfortable as possible.[25] Palliative care is not consistently defined, hence a multiplicity of definitions exist alongside each other.[26,27] A multidisciplinary, person-centered and holistic approach forms the core, as is illustrated in one of the most widely used and cited definitions of palliative care formulated by the World Health Organization (WHO) in 2002:[28,29] 'Palliative care is 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 the relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.' The WHO definition continues by adding some core principles. Palliative care provides relief from pain and other distressing symptoms, affirms life, and regards dying as a normal process, intending neither to hasten nor postpone death. It integrates the psychological and spiritual aspects of patient care and offers a support system to help patients live as actively as possible until death. It uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated. Palliative care can enhance quality of life, and may positively influence the course of illness.[29]

Historically, palliative care originated in the oncology setting as care for cancer patients nearing the end of life and until today, cancer patients remain the largest disease group receiving palliative care in many countries.[30,31] During the early phase of the modern hospice movement and for the following decades, 'homes for the dying' were predominantly designated to accommodate terminal cancer patients for whom all active treatments had ended. It is now widely acknowledged in research, practice and policy that palliative care is not limited to terminal disease, and that it has been proved to be most effective when initiated early in the course of the patient's illness without requiring the discontinuation of life-prolonging therapies or a threshold of expected survival. Influential studies by Temel et al.[32] and others,[33,34] for example, have shown that earlier integration of (specialist) palliative care into oncology care improves both quality of life and quality of care. A newer model of care has replaced the traditional 'transition' model of care (Lynn and Adamson, 2003), which presumed a clear cut-off between curative or life-extending treatment, and a terminal phase in which palliative care is initiated.[35] The new 'trajectory' model integrates curative/life-prolonging therapy and palliative care, where palliative care is regarded as a continuum. It is introduced when a life-limiting illness such as cancer is diagnosed, and becomes increasingly important as the illness progresses, responsive to individual patient needs and preferences. The initial emphasis on curative treatments decreases gradually and shifts to an emphasis on relief of symptoms and psychosocial support for patients and their caregivers.[35]

1.2.3 End-of-life care

The terms 'palliative' and 'palliation' are often equated with the provision of end-of-life care; however, palliative care and end-of-life care are overlapping but not identical concepts. Palliative care includes care provided at the end of life, but also entails much more. As described in the previous paragraph, it is part of the treatment plan from the time of diagnosis until death, and encompasses the full spectrum of care – medical, nursing, psychological, social, cultural and spiritual – for patients suffering from serious, life-threatening illness, which may be incurable.[36] End-of-life care more narrowly refers to care occurring in the final phase of a patient's life, generally in the last couple of months.[37-39] The time frame of the end-of-life period depends strongly on the underlying diagnosis and clinical course and is of course difficult to predict in many cases. In the context of this dissertation, we opted for a pragmatic definition of end-of-life care referring to all care directed towards the treatment and support of people with advanced cancer who are nearing the end of their life, regardless of whether the care one receives is palliative in nature or life-prolonging.

1.2.4 Providers of palliative and end-of-life care: generalist and specialist palliative care

As the number of people with advanced cancer rises and the likely trajectory of their disease course elongates, increasingly more healthcare professionals offer care to people with advanced cancer.[40] Regardless of the care setting, palliative care can be provided through skills at the generalist level and at the specialist level. Although palliative care is not infrequently misconceived as only referring to specialist palliative care, not every person needs a specialist to receive appropriate care, and most care for people with life-threatening illness and those nearing the end of life occurs in a primary care setting.[41-43] Considering the pressure to control healthcare costs in many countries, it is unlikely that specialist palliative care services would be capable of meeting the needs of the growing older adult population with a higher prevalence of health issues such as cancer. An appropriate combination of generalist and specialist palliative care appears a more sustainable and cost-effective solution for optimal coverage of the population in need of palliative care.[41,44,45]

Generalist palliative care – also called 'primary' or 'basic' palliative care – is typically provided by regular caregivers who have some clinical experience and basic training in palliative care, but who do not have a core identity as palliative care provider. It can be considered best practice for any clinician of any discipline who is caring for a patient with a serious illness in primary and community settings, hospital units and wards.[46,47] In many countries, general practitioners (GPs) – also called family physicians or primary care physicians – are the main providers of generalist palliative care, and often the first point of call for patients in the health system. They are responsible for the coordination and continuity of care, healthcare decision-making and referral to secondary or tertiary medical care.[48] Because of their ability to build enduring relationships with patients and families, GPs often have a good overview of the living conditions of their patients, of their needs (physical, psychosocial, etc.) and of their potential support systems. Other examples of generalist palliative care providers are oncologists, nursing staff and social workers. Although their clinical practice does not focus mainly on palliative care, they are concerned with the quality of life of patients throughout their illness journey. This includes introducing palliative care timely, responding to the patient's palliative care needs (e.g., symptom relief, emotional distress and communication with patients and families) and revisiting these needs as an individual enters the more severe stages of illness. In complex and challenging circumstances, these caregivers will seek specialist advice or offer referral to secondary specialist palliative care services.[49]

Specialist palliative care providers are professionals whose prime responsibility is the provision of palliative care. They have obtained expert knowledge, competences and specific formal training to serve the goals of palliative care.[46] Specific roles and tasks vary by country; in most countries specialist palliative care is provided in the context of a specialist multidisciplinary team dedicated to palliative and end-of-life care. When such a team is involved, patients usually continue to receive ongoing care from their main physician or clinical team, although a patient can be referred to a specialist team for continuous care in particularly demanding cases. Specialist palliative care teams can have a consulting role for patients in hospitals, hospices, at home or in nursing homes at their request, but as said, this differs across countries and even regions.[50]

Evidence from previous work shows that cancer patients have higher chances of using specialist palliative care services than patients with non-cancer diseases, and that cancer patients are being referred earlier to specialist palliative care.[51,52] A cross-national retrospective survey in four European countries (Belgium, the Netherlands, Spain and Italy) found that a cancer diagnosis, as opposed to a non-cancer diagnosis, was associated with a higher likelihood of receiving specialist palliative care in all countries except for the Netherlands, and in Belgium and the Netherlands with higher chances of an early initiation of specialist palliative care.[31]

1.2.5 Palliative care in medical oncology

In its position paper on supportive and palliative care, the European Society for Medical Oncology (ESMO) Supportive Care Faculty presents the concept of patient-centered care along with key essentials and areas for additional work.[53] The paper emphasizes that the multidisciplinary team caring for patients should ensure that patients can voice their needs (which may vary depending of the stage of the illness and will often evolve over time) and shows multiple examples of important patient-centered care interventions with regard to assessment, monitoring and management strategies, such as the assessment, monitoring and management of cancer- and treatment-related symptoms and psychological distress, preferable assessed with patient-reported outcomes (PROMs); support in increasing understanding the disease/diagnosis, options for treatment (and their limits) and prognosis, and information provision to patient and caregivers; supporting decisional processes of the patient and family, e.g., treatment decision-making and advance care planning; and preparation for the end of life and the process of dying. ESMO states that 'despite growing awareness of the need to develop patient-centered care and recent progress in the field, more and better scientific evidence, tailored to the individual and fluctuating patient needs is required so that effective interventions can be proposed to cancer patients at each stage of their illness.'[53]

The white paper of the European Association for Palliative Care (EAPC) also mentions the provision of suitable information about the illness, treatment and care options; support in individual care planning and decision-making; good communication skills; priorities/dimensions of quality of life (which can shift when the disease progresses); and a multidisciplinary approach as being common and important principles of palliative care.[9]

In the United States, the American Society of Clinical Oncology (ASCO) and the American Academy of Hospice and Palliative Medicine (AAHMP) worked together in order to create a consensus definition of what comprises high-quality primary palliative care in medical oncology. An expert group outlined a large number of palliative care service items, in nine separate palliative care domains that were based on pre-existing frameworks. Each service item was rated by 31 multidisciplinary panelists on importance, feasibility and scope within medical oncology practice. Panelists endorsed the biggest part of palliative care service items in the domains of symptom assessment and management (there was consensus that all symptoms should be assessed and managed at a basis level, with more extensive management for particularly prevalent symptoms such as dyspnea and pain); communication; advance care planning and end-of-life care.[54]

Among others, the above examples illustrate that symptom management with honest and compassionate patient-physician communication continue to be considered foundational skills that healthcare professionals need to help patients with advanced illness live as well and fully as possible, and that are central to the successful development and implementation of integrated palliative care strategies.

An important paper is the *Lancet Oncology* Commission paper (2018) authored by Kaasa and colleagues, providing recommendations from a large international expert commission (i.e., 30 experts in oncology, palliative care, public health and psycho-oncology) on how to strengthen the integration of oncology and palliative care, based on current findings on palliative care research. The Commission questions the traditional, dualistic view of treating either the tumor or the person by discussing how two distinct paradigms – the tumor-directed approach, with a main focus on treating the disease, and the host-directed approach, with a focus on the patient who has the disease – should be merged and combined to achieve the best outcome of care, if cure is no longer an option. Previous randomized trials have shown various benefits of integration of oncology and palliative care, including improved survival and symptom management, lower levels of anxiety and depression, lower risk of receiving 'futile' (potentially inappropriate) chemotherapy at the end of life, increased family satisfaction and better use of healthcare resources. Patient-directed care is provided by palliative care services in earlier stages of disease alongside tumor-directed medical care, supporting person-centered care. Routine assessment, the use of patient-reported outcomes (PROs) and active patient participation in decision-making about cancer care contribute to better symptom control, better physical health and mental wellbeing and improved use of health-care resources. Significant barriers to effective integration are a lack of international agreement on the content and standards of organization, education, and palliative care research in oncology. Further barriers include the misconception that palliative care is only for terminal patients, stigmatization of death and dying and inadequate infrastructure and funding. At a wider level, the absence of a clear set of priorities can impede integration. The Commission calls for rethinking and reorganization of cancer and palliative care delivery to promote collaboration at different care levels and to improve treatment. It advocates for changes at the system level in which the activities of professionals are coordinated to help develop and implement new, improved education programs in oncology and palliative care. The Commission also proposes the use of standardized clinical care pathways and multidisciplinary teams (in which primary, secondary and tertiary palliative care providers can get together to deliberate and in which patients can be referred, if needed) to foster integration. In order to be really effective, achieved integration needs to be anchored/secured by management and policy makers at all healthcare levels, followed by sufficient source allocation, a willingness to prioritize goals and needs and to invest/aid in generating support for more optimal integration. This integrated model should be reflected in international and national cancer care plans. It must also be succeeded by the realization of new models of care, education and research programs, all of which must be adjusted to their specific cultural setting. Independent of the prognosis of the patient and treatment intention, patient-centered care needs to be an integrated part of oncological care, based upon shifts in professional cultures and priorities in healthcare delivery.[55]

1.3 SYMPTOM BURDEN AND QUALITY OF LIFE

1.3.1 Cancer-related symptoms

The diagnosis and treatment of an advanced, life-limiting illness are stressful experiences and may have far-reaching consequences for the well-being of patients.[56] People with advanced cancer frequently experience devastating symptoms arising from the illness itself and its progression or from cancer treatment, which may gradually get worse over time and interfere with everyday functioning.[2,57-59] A systematic review of 46 studies demonstrated that more than half of patients with advanced cancer are confronted with pain, fatigue and loss of appetite.[60] Another study showed that the quality of life of nearly all European patients with advanced cancer is reduced because they have at least one symptom, for example pain, appetite loss, insomnia, nausea or/and constipation.[58] Advanced cancer also has a profound impact on mental health. Many patients suffer from the emotional effects of their illness, such as depression and anxiety.[61,62] Cancer symptoms and quality of life issues are – and should continue to be – among the highest priorities of oncology clinicians and researchers,[63] however, the fact that the prevalence of physical as well as psychological cancer-related symptoms remains high suggests that these symptoms are not always adequately managed.[64] Uncontrolled symptoms can be very distressing for patients, hampering the performance of daily activities of an individual and adversely affecting many other aspects of their (quality of) life.[57,59,62]

1.3.2 Quality of life

Increasing overall survival has long been the primary focus of cancer treatment, but it is now generally acknowledged that preserving quality of life (QoL) is a very important endpoint and a major goal for patients with advanced cancer.[65] QoL has been defined by the World Health Organization (WHO) as 'an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, standards and concerns.'[66] The WHO further describes QoL as 'a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment.'[66] Monitoring cancer-related symptoms and QoL is crucial to enable healthcare providers to better react to patients' changing needs.[67-69] QoL has therefore become a frequent topic of research. Assessments (surveys, questionnaires, scales) and symptom tracking are used by researchers to measure QoL. Information can be collected directly from the patient (patient-reported data) or researchers may collect feedback from other sources such as caregivers, although asking healthcare professionals or relatives has shown to be a less accurate strategy to assess QoL than asking patients themselves.[67,70]

1.3.3 Symptom burden and quality of life across countries and over time: need for further research

Maintaining or improving QoL and providing relief to patients from distressing symptoms are crucial outcomes of palliative care.[71] Adequate monitoring of these outcomes is needed to inform and guide person-centered care. To better understand symptom burden and QoL in advanced cancer patients and plan more effective symptom management, there is a need for more knowledge about the experience of symptoms from the patient's perspective. Various previous studies have focused on the topic of symptom burden and/or QoL in advanced cancer populations, yet the work is anything but over. Most prior studies have small sample sizes or are limited to relatively small geographical areas. Therefore, still little is known about cross-country differences in these key outcomes. Advanced cancer is a big societal challenge across many nations and regions. Europe has a very high disease burden of cancer; in 2016, more than one in four deaths (26%) could be attributed to cancer, which makes it the second leading cause of death behind cardiovascular disease. In some European countries, including Denmark, the Netherlands and the United Kingdom (UK), the number of cancer deaths has already surpassed heart disease as the most common cause of death.[72] Considering that contextual factors such as cultural, ethical and legal context and aspects of healthcare systems vary between countries, we believe that studying cross-national differences in symptom burden and QoL could be useful for a better understanding of how people with advanced cancer are cared for in our own country and in other European countries, and for identifying possible areas for improvement. Furthermore, we think that, because good-quality palliative requires optimal symptom control and support at *any* point along the advanced illness trajectory and towards the end of life, it is important to assess functional status, symptom burden and QoL not only cross-sectionally but also over an extended period of time (with repeated registrations as the illness progresses).

1.4 COMMUNICATION AND INFORMATION PROVISION AT THE END OF LIFE

1.4.1 Patient-centered communication and the discussion of end-of-life topics

Communication is a core skill to master in clinical practice for all physicians who care for patients and families facing advanced illness. Several decades ago the principle of medical paternalism (a philosophy that implies that the physician decides which course of action is most appropriate, based on what he/she believes to be in the patient's best interest)[73] was highly valued. At present, the more liberal idea that individuals should be free to make their own choices about their lives has become more and more eminent. The emphasis is on personal autonomy and self-determination.[74] In this light, good-quality palliative care requires that physicians engage in patient-centered communication, which involves respecting the patient as an individual, directing patients to the care they need when they need it, providing timely, adequate and understandable information, supporting involvement in decision-making and making decisions consistent with patients' values.[75,76] There are many advantages of effective communication, including better understanding of the illness, care and treatment options,[77] adherence to therapeutic regimens[78,79] and satisfaction with end-of-life care.[78,80] Nonetheless, multiple barriers exist in communication with patients and their families, and throughout recent decades there have been consistent findings that patients' communication, information and support needs are not always met in cancer care.[81] Poor communication can have significant consequences such as adverse mental health outcomes, worsening of symptoms,[82] and more aggressive, unwanted life-prolonging care.[83]

It has been estimated that less than 40% of people with advanced cancer have conversations about topics related to end-of-life care (e.g., diagnosis, treatment preferences, psychosocial issues) with a physician.[83,84] Discussions about end-of-life planning have numerous beneficial effects for patients and their caregivers. Patients who have discussed their preferences for end-of-life care with physicians are more likely to choose palliation over aggressive medical care near death (less aggressive care at the end of life is associated with better QoL), to die at home or in a hospice, and to receive care that is aligned with their preferences.[83,85,86,87]

1.4.2 The discussion of end-of-life topics: need for further research

Communication regarding end-of-life care in oncology oftentimes is perceived as infrequent and suboptimal.[88,89] Possible barriers to engage in effective end-of-life communication include a general reluctance to talk about death and dying, lacking knowledge and training in this area, and inadequate structural support for advance care planning (ACP).[90,91] Person-centered communication and ACP have received increasing policy attention in Europe over the last years, and several European countries have made efforts in this area by putting training, programs and guidelines for palliative care into practice. In view of these developments and given the adverse outcomes associated with not having end-of-life discussions, the question is raised whether there has been a significant increase over time in conversations with European cancer patients about topics related to end-of-life care – especially in primary care, since GPs provide care across the life-course and are well suited to initiate end-of-life conversations with their patients. There is little comparable, empirical evidence on the content and frequency of end-of-life care communication practices among people with cancer in Europe. Contextual circumstances such as culture, healthcare system organization, resource ability or attitudes towards the end of life may affect such practices. Cross-country comparative studies are worthwhile because they can inform national and international policies by drawing attention to factors that are universally important and those that are country specific.

1.4.3 Information provision and shared decision-making

People with life-threatening illness face hard decisions. There is wide-ranging agreement that people should be informed about healthcare options and involved in decisions about their own care. Enabling people to make informed choices about their own care and provide care that is in line with a person's preferences have been core values of palliative care since its inception.[81] To be active participants in their care, patients with life-threatening illness and their families must have an adequate understanding of their illness, treatment and care options. Substantial variation exists across individuals in their preferences for information,[92,93] and personal values and capabilities should always be taken into account when tailoring (the amount of) information to patients and when engaging people in healthcare decision-making.[94] However, the clear majority of cancer patients today report a preference for detailed information about their condition, and according to a systematic review of information and decision-making preferences in people with advanced cancer, approximately two-thirds wants to be actively involved in decision-making about their care.[95]

1.4.4 Information provision and shared decision-making: need for further research

Specialist palliative care providers are committed and specifically trained in supporting patients in the final phase of life. It would be expected that these specialists pay a considerable amount of attention to optimizing the provision of information to their patients, and that those being guided by specialist palliative care services are given the opportunity to be actively involved in decision-making. As far as we know, research to date has not yet investigated the provision of information – also regarding end-of-life care – to cancer patients and those close to them by different types of specialist palliative care services. Studying the perspectives of both cancer patients and relatives of (deceased) cancer patients is valuable, because family members are often actively involved in care for a patient at the end of life. Many patients prefer medical decisions to be made jointly with their family and oncologist,[96] and when a dying patient is no longer able to make his or her own decisions, relatives usually become the primary communicators with healthcare and palliative care professionals regarding healthcare-related decisions.[97,98] Therefore, it is very important that relatives are provided with sufficient and accurate information.

1.5 END-OF-LIFE DECISION-MAKING

1.5.1 Potentially life-shortening end-of-life decisions

When death approaches, the goals of medical care need to be adjusted. The patient's comfort is more than ever key to all decisions about treatment and care.[99] In the WHO definition of palliative care, hastening of death is stated not to be among the intentions of palliative care.[29] Nevertheless, efforts to improve the patient's comfort can lead, though rarely, to the (possible) hastening of death,[100] mostly as a foreseen but unintended consequence of decisions to refrain from potentially life-extending but burdensome interventions (non-treatment decisions) or to use highly dosed medication to relieve severe pain (intensifying pain or symptom alleviation). In some occasions, hastening of death may be an appreciated or even explicitly intended outcome, when the patient is experiencing unbearable suffering with no prospect of improvement (euthanasia, physician-assisted suicide or life-shortening without the individual's explicit request).[101] Former research has shown that end-of-life decisions with a possible or certain life-shortening effect (ELDs) – specifically intensified symptom alleviation, euthanasia and physician-assisted suicide – are more prevalent in cancer patients than in non-cancer patients.[102-105] Possible reasons may be a higher symptom burden in cancer,[106,107] better availability or accessibility of palliative care services[108-110] and an increasing trend in cancer care toward more disclosure of both cancer diagnosis and prognosis, which may result in more ELDs.[2]

1.5.2 Potentially life-shortening end-of-life decisions: need for further research

ELDs in cancer patients have been described by several prior studies,[99,102,104,111] but to our knowledge, none have investigated the occurrence of ELDs and characteristics of the decision-making process across cancer types. Looking at differences across cancer types is informative because it is known from earlier studies that patients with different types of cancer do not always receive the same types and intensity of end-of-life care (e.g., hematological cancer in particular has been associated with poorer access to palliative care services and higher likelihood of receiving aggressive intensive care unit treatment, and with lower likelihood of dying at home in comparison to solid malignancies).[112-120] If such variation across cancer types also exists regarding the prevalence of ELDs and aspects of the decision-making process, this might be an indication of inequity in the provision of end-of-life care to people with advanced cancer. The findings could help inform policy and practice about whether tailoring terminal care to specific cancer diagnoses is desirable.

1.6 STUDY OBJECTIVES AND RESEARCH QUESTIONS

Three objectives, each with specific research questions, guide this dissertation.

The ***first objective*** is to evaluate self-reported emotional and physical functioning, symptoms and quality of life in people with advanced cancer. The research questions are:

1. What is the patient-reported emotional and physical functioning, symptom intensity and overall quality of life in people with advanced cancer in six European countries, and are there differences between countries? (**Chapter 2**)
2. How do patient-reported emotional and physical functioning, symptom intensity and overall quality of life differ between cancer patients receiving palliative care in Europe, and how do these outcomes progress over time? (**Chapter 3**)

The ***second objective*** is to evaluate end-of-life communication and information provision in people with advanced cancer. The research questions are:

3. Are there trends over time in communication about end-of-life topics with cancer patients in general practice in three European countries, and are there differences in time trends in GP-patient end-of-life communication with respect to the patients' age at death, gender, cancer type, place of residence in the last year of life and place of death? (**Chapter 4**)
4. How do people with cancer being supported by specialist palliative care services evaluate information provision and their involvement in decision-making, how do bereaved relatives of cancer patients who received care of specialist palliative care services evaluate information provision, and do these evaluations differ depending on patient characteristics, length of guidance and the type of palliative care service? (**Chapter 5**)

The ***third objective*** is to examine end-of-life decisions and the preceding decision-making process in people who died from cancer. The research question is:

5. What is the prevalence and what are the characteristics of end-of-life decisions in different cancer types? (**Chapter 6**)

1.7 METHODS

Different data collections were used to address the study objectives and research questions of the dissertation.

1.7.1 Cross-sectional survey among people with advanced cancer: baseline data from an international multicenter cluster-randomized trial among people with advanced cancer (Chapter 2)

To address ***research question 1***, we used baseline patient data from the *ACTION trial*, a multicenter cluster-randomized controlled trial carried out in 23 hospitals in six European countries (Belgium, Denmark, Italy, the Netherlands, Slovenia, United Kingdom). Per country and per pair of comparable hospitals (academic or non-academic), hospitals were randomized to either the intervention arm, providing 'usual care' supplemented with a structured advance care planning (ACP) program, or to the control arm, offering 'usual care' only. Competent patients with advanced lung (stage III or IV) or colorectal cancer (stage IV) or metachronous metastases who were deemed eligible by members of their healthcare team informed of the study and invited to participate. Lung and colorectal cancer patients were selected for the study because these cancers have high incidence and death rates in Europe and affect both sexes.[121,122]

In both trial arms, included patients were followed until one year after entering the study. They were asked to complete and return a pen-and-paper questionnaire at baseline – i.e., the moment of inclusion, prior to delivery of the ACP program to the intervention group – and again at 11-12 weeks, and 19-20 weeks post-inclusion. Only baseline data are reported in the study included in this dissertation. Patients completed socio-demographic items on their age, education, gender, living situation and religiosity. Treating physicians or other healthcare professionals delivered clinical background information on the primary diagnosis, current stage of the disease, time since first diagnosis of the primary tumor, time since diagnosis of the current cancer stage, and the patient's cancer treatment(s) at baseline.[121,122]

All relevant outcome variables were assessed using the palliative care version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C15-PAL).[123] This measurement tool is a shortened version of the EORTC QLQ-30 core questionnaire for measuring QoL in cancer patients.[124]

Ethical considerations

The ACTION trial was registered in the International Standard Randomised Controlled Trial Number (ISRCTN63110516) as of 10 March 2014. Ethical committee procedures were followed and approval was obtained in all countries and institutions involved. Patients who were deemed eligible by their care team and willing to consider possible participation were provided with more information about the study by the research team. Patients were given unrestricted time to consider participation and were informed that they were free to withdraw from participating in the study without any effect on their care. Prior to study enrollment, each participant in this study gave written informed consent to take part in the research. All study participants agreed to the use of their (anonymized) data as outlined in the information given to them prior to study start.

1.7.2 International multicenter longitudinal study among people with cancer enrolled in palliative care (Chapter 3)

We drew on data from the multicenter longitudinal *European Palliative Care Cancer Symptom (EPCCS) study* in order to answer ***research question 2***. The EPCCS study was conducted between April 2011 and October 2013 in 30 palliative care centers in 12 countries (Australia, Belgium, Canada, Denmark, Georgia, Germany, Italy, Norway, Portugal, Spain, Switzerland and United Kingdom). A large number of patients with advanced, incurable cancer were included – all were defined as a palliative care patient, enrolled in a palliative care program. Patients who were receiving treatment with a curative intent were excluded.[125]

The data we used were collected through a case report form on medical data completed by healthcare providers (HCP-CRF) and by participants' self-report on health and symptoms (patient-CRF). Both CRFs were completed monthly (3-5 weeks) for a minimum of three months, or until death or study withdrawal. The HCP-CRF consisted of a brief set of medical and treatment-related variables, e.g., primary cancer diagnosis, comorbidities, anti-cancer treatment and medications. A retrospective recording of date of death was performed in each study center approximately six months after the last study inclusion. The patient-CRF consisted of key socio-demographic characteristics, e.g., age, gender, marital status, living situation and education (collected at baseline), and questions on quality of life (QoL) and symptom severity.[125] The variables of interest in our case were overall quality of life, emotional functioning, physical functioning and cancer-related symptoms as assessed by the palliative care version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C15-PAL).[123]

Ethical considerations

The study was performed according to the Declaration of Helsinki and was registered in the ClinicalTrial.gov database (no. NCT01362816). Ethical approval was obtained at each site and all participants gave written informed consent prior to study start.

1.7.3 Mortality follow-back study among general practitioners (GPs) of cancer patients in representative epidemiological surveillance networks (Chapter 4)

The data used to address ***research question 3*** were collected in Belgium, the Netherlands and Spain (Castile and León) as part of the *European Sentinel Network Monitoring End-of-Life Care (EURO SENTIMELC)* study. The EURO SENTIMELC study is an ongoing mortality follow-back study designed to retrospectively monitor end-of-life care in population-based samples of deaths in different countries.[126] The study was conducted in 2009-2010 (Spain: 2010-2011) and 2013-2014 among general practitioners (GPs) in representative GP Sentinel Networks: epidemiological surveillance networks consisting of GP practices or community-based physicians who voluntarily and continuously monitor health problems existing in the population.[31] In each country, GPs were selected to form a representative national sample of the total GP population and invited to participate in the networks by national public health and/or research institutes.

Participating GPs provided weekly reports on every adult patient in their practice who had died during the past week as part of a larger public health questionnaire. In order to answer ***research question 3***, we included all people registered by the participating GP practices who died of cancer (coded according to ICD-10). People whose death was classified by the GPs as 'sudden and totally unexpected' and those for whom this information was missing were excluded, leaving a sample that was eligible for palliative care.

Using a standardized registration form consisting of structured and closed-ended items, GPs collected demographic characteristics (age at death, gender, longest place of residence in the last year of life, place of death), cancer type and whether or not death was sudden and unexpected. Additionally, they reported for five end-of-life care topics (diagnosis, options for end-of-life care, psychological or social problems, the patient's preference for medical treatment and the patient's preference for a proxy decision-maker) whether they had been discussed with the patient.

Ethical considerations

For Belgium, ethics approval was obtained from the Ethical Review Board of Brussels University Hospital of the Vrije Universiteit Brussel (VUB). Formal approval for this research project by a medical ethics committee was not required in The Netherlands according to the Medical Research (Human Subjects) Act (WMO), but permission for the study was sought and obtained from the board of the NIVEL network. The NIVEL Primary Care Database extracts data according to strict guidelines for the privacy protection of patients and GPs. Ethics approval was not required for posthumous collection of anonymous patient data in Spain, according to the legislation of this country.

1.7.4 Nationwide cross-sectional survey of 34 specialist palliative care teams (Chapter 5)

In order to examine ***research question 4***, we used data from a nationwide cross-sectional survey that was part of the more comprehensive *Quality Indicators for Palliative Care (QPAC) study*.[127-129] Questionnaires were administered at one moment in time during four measurement periods (November 2014, May 2015, November 2015 and May 2016) within 34 specialist palliative care services (PCSs).

Our current study focuses on the survey questions related to information provision as evaluated by patients and relatives. Only those with a diagnosis of cancer were included in the analyses. Data from two different respondent groups were studied: 1) cancer patients being guided by specialist palliative care services (PCSs) at the time of the measurement, and 2) the people most relevant to patients who had died of cancer (e.g., partner, family member or friend most closely involved). People with cancer and bereaved relatives were identified based on the questionnaire for patients (question about main diagnosis) and on checklists that were completed by the coordinators of the participating palliative care teams for all patients included in the measurement. These checklists contained information about the diagnosis (cancer/non-cancer), demographic information (age, gender), date of referral to the PCSs and the date of death for those who had already died. Checklist and questionnaire data were linked using unique anonymized identification numbers.

The measurement procedure followed a snapshot approach. A cross-sectional inclusion method was used during every measurement period which required the palliative care teams to make a random selection of two groups of patients on one given day (i.e., the day of the assessment), with a maximum of 50 in each group: people who were under the guidance of PCSs on that specific day and people who had died while under the guidance of PCSs between the previous four weeks and four months.[127] For the first group, questionnaires were sent to the persons with cancer (or to a representative if they were unable to fill out the questionnaire). For the second group, questionnaires were sent to the most significant relatives, mostly the partners. Completed questionnaires were gathered by the palliative care teams and sent to the researchers for data analysis.

The questionnaire items related to information provision were either based on existing questionnaires or developed by the researchers in cooperation with an expert panel.[129] Items were mainly derived from the CQ-index Palliative Care, a structured questionnaire containing questions on care experiences and consisting of a patient version and a relative version.[130,131]

Ethical considerations

At inclusion, all respondents received a questionnaire and a covering letter (including a request for informed consent) providing information about the purpose and the voluntary character of participation in the study. Since the palliative care teams were responsible for the distribution of questionnaires and anonymous numbers were used for each participant, the completed questionnaires received by the researchers could never be linked to the identifying information and anonymity was preserved at all times. The protocol of the entire measurement procedure and data collection was approved by the Ethical Review Board of Brussels University Hospital of the Vrije Universiteit Brussel (VUB) and by the local ethical board of every hospital participating in the measurement.

1.7.5 Retrospective survey among treating physicians based on death certificates (Chapter 6)

Data from the *death certificate study on end-of-life decisions (ELD study)* based on a representative sample of deaths in Flanders, Belgium, were used to address ***research question 5***. Between 1 January and 30 June 2013, a random sample of all deaths of Belgian residents (aged 1 year or older) was drawn weekly by the Flemish Agency for Care and Health (FACH) – the central administration authority for processing death certificates. Before sampling, the deaths were stratified for the likelihood that an end-of-life decision (ELD, a decision with a possible or certain life-shortening effect) had preceded death based on the cause of death; i.e., larger samples of deaths were taken for strata in which the cause of death made and ELD more likely.[132] For our analysis all deaths in the database with an underlying cause of cancer were selected.

Certifying physicians were sent a four-page questionnaire via standard mail within 2 months of the death concerning medical decisions made at the end of life, the decision-making process, and the care provided. They were requested to complete the questionnaire by consulting the patient's medical file. If the certifying physician was not the treating physician, the questionnaire was passed on to the treating physician.

Tested thoroughly by a panel of physicians, the questionnaire was largely identical to those of previous studies in Belgium, the Netherlands and other European countries, the first of which had been developed for the 1990 Dutch survey on ELDs.[133] The questionnaire first asked whether death had been sudden and unexpected and whether the attending physician's first contact with the patient had been after death. If the answer to both these questions was no – hence end-of-life decision-making before death was not precluded – they were then asked whether they had (1) withheld or withdrawn life-prolonging medical treatment (e.g., chemotherapy, artificial provision of nutrition and hydration, provision of antibiotics, and mechanical ventilation) taking into account or explicitly intending the hastening of death (non-treatment decision); (2) intensified the alleviation of pain and/or other symptoms with drugs with the possibility of hastening death (intensified alleviation of pain and symptoms); or (3) administered, supplied or prescribed drugs with the explicit intention of hastening death. If in the latter case someone other than the patient at the patient's explicit request had administered the drugs, the act was classified as euthanasia; if drugs had been prescribed or supplied and self-administered, the act was classified as physician-assisted suicide. If there had been no explicit request from the patient, the act was classified as life abbreviation without explicit patient request. For patients for whom more than one ELD was made, the act with the most explicit life-shortening intention was regarded as the most important ELD. When two decisions with similar life-shortening intention were made, administering drugs was regarded as prevailing over withholding or withdrawing treatment as the most important ELD. Questions then followed about the reasons for the most important ELD and about the decision-making process (the involvement of the patient, family, and professional caregivers in making the decision).

Data on sex, age, place, and underlying cause of death were available from the individually linked death certificate information. The underlying cause of death variable was coded according to ICD-10. People dying from cancer were identified according to ICD-10 codes C00 to C97.

Ethical considerations

To guarantee absolute anonymity, a lawyer served as intermediary between responding physicians, researchers, and the FACH ensured that completed questionnaires could never be linked to a particular patient or physician. The mailing and anonymity procedures 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. Ethical approval was obtained from the Ethical Review Board of the University Hospital of the Vrije Universiteit Brussel (ref no. 143201316288, 8 February 2013). Patients were deceased, and consent was not required. Physicians' participation was regarded as implicit consent, which was noted in the accompanying letter introducing the study.[132,134]

1.8 DISSERTATION OUTLINE

Following this general introduction, **Chapters 2 to 6** of the dissertation are based on articles that have been published in scientific peer-reviewed journals. All chapters can be read independently.

PART I of this dissertation focuses on self-reported emotional and physical functioning, symptoms and quality of life in people with advanced cancer (***first objective***). **Chapter 2** describes emotional functioning, physical functioning, symptom intensity and overall quality of life as reported by advanced cancer patients in six European countries, and digs into cross-country differences. **Chapter 3** provides insight into the course (evolvement) of emotional functioning, physical functioning, symptom intensity and overall quality of life over time in an international sample of cancer patients enrolled in palliative care.

PART II concerns end-of-life communication and information provision in people with advanced cancer (***second objective***). **Chapter 4** investigates time trends in GP-patient end-of-life communication with cancer patients in general practice in three European countries, and whether time trends differ depending on the patients' age at death, gender, cancer type, place of residence in the last year of life and place of death. **Chapter 5** explores how cancer patients being supported by specialist palliative care services evaluate information provision and involvement in decision-making, how relatives of cancer patients who had died while under the guidance of specialist palliative care services evaluate information provision, and how evaluations may vary with respect to the patient's age and gender, length of guidance, and the type of palliative care service.

PART III is devoted to end-of-life decisions and the preceding decision-making process in people who died from cancer (***third objective***). **Chapter 6** concentrates on the prevalence of end-of-life decisions, characteristics of end-of-life decisions and characteristics of the preceding decision-making process in people with cancer, and examines differences across cancer types.

Table 1: Overview of the aims and methods used in each chapter of the dissertation

	Study objectives and research questions (RQ)	Method
PART I		
Chapter 2	***First objective:* to evaluate self-reported emotional and physical functioning, symptoms and quality of life in people with advanced cancer.** *RQ1.* What is the patient-reported emotional and physical functioning, symptom intensity and overall quality of life in people with advanced cancer in six European countries, and are there differences between countries?	International cross-sectional study *Based on the ACTION study in six European countries*
Chapter 3	***First objective:* to evaluate self-reported emotional and physical functioning, symptoms and quality of life in people with advanced cancer** *RQ2.* How do patient-reported emotional and physical functioning, symptom intensity and overall quality of life differ between cancer patients receiving palliative care in Europe, and how do these outcomes progress over time?	International longitudinal study *Based on the EPCCS study in 12 countries*
PART II		
Chapter 4	***Second objective:* to evaluate end-of-life communication and information provision in people with advanced cancer**. *RQ3.* Are there trends over time in communication about end-of-life topics with cancer patients in general practice in three European countries, and are there differences in time trends in GP-patient and end-of-life communication with respect to the patients' age at death, gender, cancer type, place of residence in the last year of life and place of death?	Mortality follow-back study *Based on the EURO SENTIMELC study in Belgium, the Netherlands and Spain*
Chapter 5	***Second objective:* to evaluate end-of-life communication and information provision for people with advanced cancer.** *RQ4.* How do people with cancer being supported by specialist palliative care services evaluate information provision and their involvement in decision-making, how do bereaved relatives of cancer patients who received care of specialist palliative care services evaluate information provision, and do these evaluations differ depending on patient characteristics, length of guidance and the type of palliative care service?	Nationwide retrospective cross-sectional study *Based on the QPAC study in Flanders, Belgium*
PART III		
Chapter 6	***Third objective:* to examine end-of-life decisions and the preceding decision-making process in people who died from cancer.** *RQ5.* What is the prevalence and what are the characteristics of end-of-life decisions in different cancer types?	Nationwide retrospective death certificate study *Based on the ELD study in Flanders, Belgium*

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Part I

Self-reported emotional and physical functioning, symptoms and quality of life in people with advanced cancer

2

Functional impairment, symptom severity and overall quality of life in patients with advanced lung or colorectal cancer in six European countries: baseline findings from the ACTION study

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This chapter is also published as an article in: *Supportive Care in Cancer* 2021; **29**(10): 5797-810. [2020 SCI impact factor 3.603; journal ranking Q1; ranking n°9 of 68 in REHABILITATION in SCIE edition]

ABSTRACT

Background: People with advanced cancer often suffer from various symptoms, which can arise from the cancer itself and its treatment, the illness experience and/or co-morbid conditions. Important patient-reported outcomes such as functional status, symptom severity and quality of life (QoL) might differ between countries, as countries vary with regard to contextual factors such as their healthcare system.

Purpose: To assess self-reported emotional functioning, physical functioning, symptoms and overall QoL in patients with advanced lung or colorectal cancer from six European countries, particularly in relation to their country of residence.

Methods: We used baseline patient data from the ACTION trial, including socio-demographic and clinical data as well as patient-reported data regarding functioning, symptoms and overall QoL (EORTC QLQ-C15-PAL).

Results: Data from 1,117 patients (55% lung cancer stage III/IV, 45% colorectal cancer stage IV) were used. The highest (worst) average symptom score was found for fatigue. We found similarities but also important differences in the outcomes across countries. The best scores (highest for emotional functioning and QoL, lowest for symptoms) were reported by Dutch and Danish patients. Belgian patients reported relatively low emotional functioning.

Conclusion: The optimization of functioning, symptom relief and overall QoL should be important objectives of healthcare professionals who take care of patients with advanced cancer. There are similarities, but also substantial differences across countries in functional status, symptoms and overall QoL. Policy makers should take these differences into account and invest in offering health care catered to the needs of their population.

2.1 INTRODUCTION

Despite considerable improvements in supportive cancer care, people with advanced cancer experience a large variety of burdensome symptoms. A systematic review of 46 studies demonstrated that pain, fatigue and loss of appetite occur in more than 50% of patients with advanced cancer.[1] Another study carried out among advanced cancer patients in Europe concluded that the quality of life (QoL) of virtually all patients with advanced stages of disease is impaired by symptoms such as pain, appetite loss, insomnia, nausea and constipation.[2] Symptoms can be a result of the cancer itself and its progression (e.g., site-related pain),[3] occur as adverse effects of treatment (e.g., chemotherapy- or radiation-induced fatigue, nausea and vomiting)[4,5] or arise from co-morbid conditions in addition to cancer. They may also more generally reflect aspects of the patient's experience of living with severe illness (e.g., anxiety and depressed mood).[6] Unrelieved symptoms are a source of great distress and can adversely affect a patient's function and participation in activities of daily living.[7,8]

Among all malignancies, lung and colorectal cancers are the most commonly diagnosed non-gender related cancers worldwide, contributing 12.3% and 10.6%, respectively, to the total incidence of cancer in 2018.[9] Recent estimates indicate that lung and colorectal cancers remain leading causes of cancer deaths in Europe among both men and women, having caused approximately 388,000 deaths in 2018 each.[10] Lung cancer generally has a poor prognosis since it is often diagnosed in an advanced stage, and it is known to carry a higher symptom burden and lower QoL as compared with other cancers.[11,12] Symptoms that are common in late-stage lung cancer are, for instance, pain, decreased appetite, dyspnea, cough and depression.[13,14] Advanced colorectal cancer is frequently associated with symptoms such as abdominal pain, anorexia, weight loss, nausea, gastrointestinal obstruction and weakness/lack of energy.[15,16]

A fundamental goal of palliative care is to preserve acceptable QoL as long as possible. Properly monitoring patients' functional status, symptom experience and overall health-related QoL is crucial to inform and guide patient-centered care, an ethical imperative in modern health care.[17,18] The use of patient-reported outcome measures (PROMs), often in the form of questionnaires, is an effective means of measuring different aspects of a patient's health status.[19]

Recent studies have described symptoms and/or QoL in advanced (lung and colorectal) cancer populations, but most of them are rather small samples and/or geographically limited.[20-25] Common and deadly forms of cancer – including lung and colorectal cancer – are societal challenges that are not restricted to single nations and regions. Therefore, it is important to learn more about differences between countries, where contextual factors such as the specific cultural, ethical and legal context, healthcare systems and palliative care services vary. In the current article, we present baseline data from the multicenter ACTION trial among people with advanced stages of lung or colorectal cancer treated across a wide range of different hospitals in six European countries.

The specific research questions were:

1. What is the patient-reported emotional functioning (EF) and physical functioning (PF), symptom severity and overall QoL in people with advanced lung or colorectal cancer?
2. Do EF and PF, symptom severity and overall QoL differ between patients from different European countries, when socio-demographic and clinical variables are considered?

2.2 METHODS

Study population

Patients participated in the ACTION trial, a cluster-randomized controlled trial carried out in 23 hospitals in six European countries (Belgium, Denmark, Italy, the Netherlands, Slovenia and the United Kingdom (UK)) from 2015 to 2018. Per country and per pair of comparable hospitals (academic or non-academic), hospitals were randomized to either the intervention arm, providing 'usual care' supplemented with a structured advance care planning (ACP) program, or to the control arm, offering 'usual care' only. Patients with advanced lung (stage III or IV) or colorectal cancer (stage IV or metachronous metastases) who were deemed eligible (for a precise description of the inclusion and exclusion criteria, see *Box 1*) were informed of the study and invited to participate. Further details on procedures related to the complete trial are described in a protocol paper.[26]

Box 1. Eligibility criteria for patient participation in the ACTION trial

Inclusion criteria:

1. Histologically confirmed diagnosis of:
   a. Lung cancer:
      - Small cell – extensive disease/stage III or IV*
      - Non-small cell – stage III or IV*

   b. Colorectal cancer: stage IV or metachronous metastases*
   * according to the 7th edition of the TNM Classification of Malignant Tumors standard for cancer staging and classification
2. Physically and mentally competent to give written informed consent
3. World Health Organization (WHO) performance status grade 0-3*
   * score ranging from 0 (fully active) through 3 (capable of only limited self-care) to 5 (death)
4. An estimated life expectancy of at least three months

Exclusion criteria:

1. Aged younger than 18 years
2. Unable to provide informed consent
3. Unable to complete questionnaire in the country's language
4. Taking part in a research study that is evaluating palliative care services or communication strategies

Assessments

Socio-demographic and clinical patient characteristics

In both trial arms, patients who consented were included and followed until one year after entering the study. They were asked to complete a pen-and-paper questionnaire at baseline – the moment of inclusion, prior to delivery of the ACP program to the intervention group – and again at 11-12 weeks and 19-20 weeks post-inclusion. *Baseline data from both trial arms are reported here*. Patients completed socio-demographic items on their age, education, gender, living situation and religiosity. Treating physicians or other healthcare professionals delivered clinical background information on the primary diagnosis, current stage of the disease, time since first diagnosis of the primary tumor, time since diagnosis of the current cancer stage and cancer treatment(s).

Patient-reported functioning, symptoms and overall quality of life

All relevant outcome variables were assessed using the palliative care version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C15-PAL).[27] This measurement tool is a shortened and more focused version of the EORTC QLQ-C30 core questionnaire for measuring QoL in cancer patients,[28] one of the most extensively used PROMs in oncology clinical practice settings. EF was measured by a four-item scale (the original EORTC QLQ-C30 scale); PF by a three-item scale. Symptoms were evaluated through a pain scale (two items), a fatigue scale (two items) and five single items (nausea/vomiting, dyspnea, insomnia, appetite loss, constipation). Overall QoL was measured by one item. Items related to EF, PF and symptoms used a four-point Likert-type response scale ranging from 1 'not at all' to 4 'very much'. The overall QoL item was rated on a seven-point scale from 1 'very poor' to 7 'excellent'. Responses concerned participants' experiences 'during the past week'. Scores and scale scores were calculated following the EORTC scoring manual and its addendum.[29,30] After standardization by linear transformation, scores range from 0 to 100. Higher scores on the functioning scales and overall QoL represent higher levels of functioning and higher QoL. Higher scores on symptom scales/items mark a higher symptom severity.

Statistical methods

Statistical analyses were performed using R version 3.5.1 (2018-07-02). Linear mixed models were estimated in order to explore how each outcome (EF, PF, symptoms and QoL) could be understood in terms of the patients' country of residence, taking into account other socio-demographic and clinical patient characteristics. A stepwise selection procedure was used and the analysis continued until all potential predictors were evaluated, resulting in a model for each of the outcome variables. The Netherlands (country with the highest overall QoL) was chosen as a reference category. No theoretical standard exists to determine which reference population is most 'appropriate', and the interpretation of the results can vary depending on which comparison group is chosen. To counter this concern, we implemented a second approach to analyzing the data to see whether the two parallel methods would lead to similar results. We conducted contrasts comparing each individual country's mean score to the average mean of the remaining countries, for all outcomes separately. We corrected for multiple testing across contrasts. A more detailed description of the statistical methods can be found in Appendix 1.

Descriptive statistics on socio-demographic and clinical patient characteristics are presented per country; means (and standard deviations) for continuous variables, counts (and percentages) for categorical variables. Estimated differences in means (and 95% confidence intervals) of the outcomes – functioning scales, symptoms and overall QoL – between countries are shown, adjusted for confounding variables. Differences between individual country mean scores and the average mean of the other countries (contrast testing) are also presented. A global overview of mean scores (and standard deviations) for all outcomes per country can be found in Appendix 2.

2.3 RESULTS

Characteristics of the study population

A total of 2,748 patients were asked to take part in the study, of whom 1,117 (41%) were enrolled in either the intervention or the control arm of the ACTION trial. *Table 1* shows the socio-demographic and clinical characteristics of the sample. The number of participants ranged from 97 in Slovenia to 255 in the UK. Patients had a mean age of 66.3 years (SD=9.8) at study entry. About 55% of the patients had lung cancer and 45% had colorectal cancer as their primary diagnosis, and on average patients had been diagnosed with the primary tumor 1.5 years (SD=2.2) prior to entering the study. Most patients (74%) were receiving chemotherapy at inclusion, 13% targeted therapy, 10% immunotherapy, 8% radiotherapy and 14% 'other' types of treatment.

Patient-reported emotional and physical functioning, symptom severity and overall quality of life

Altogether, participants average scores (range 0-100) at inclusion were 77.1 (SD=21.4) for EF and 81.9 (SD=21.1) for PF (*Table 2*). Fatigue was the symptom with the highest (most severe) average score (38.8, SD=26.6), followed by insomnia (27.9, SD=28.9) and dyspnea (24.8, SD=28.1). The lowest (least severe) scores were observed for nausea/vomiting (15.9, SD=24.4) and constipation (18.3, SD=27.9). The average score for overall QoL was 64.3 (SD=21.3).

Patient-reported emotional and physical functioning across countries

Figure 1 shows average EF and PF in the six different countries. After adjustment for the effects of centers (hospitals), socio-demographic and clinical patient characteristics (age, years of education, gender, primary diagnosis, years since diagnosis of current cancer stage and current cancer treatments) and compared to Dutch participants (the Netherlands = reference category), Belgian participants reported significantly lower (worse) EF (mean difference -7.5, 95% CI=-13.9; -1.1), and participants from the UK reported significantly worse PF (mean difference -8.5, 95% CI=-16.2; -0.9) (*Table 2*).

Comparison of individual country means with average means of the remaining countries (country contrasts) indicated that Belgium had a significantly lower (worse) mean score on EF than the other countries' average mean score (mean 73.3 vs. 78.0, p = .04). Denmark, on the contrary, had a significantly higher mean score on EF compared to the average of others (mean 81.6 vs. 76.3, p = .04) (*Table 3*).

Patient-reported symptom severity across countries

Figure 2 shows average symptom severity per symptom in the different countries. Compared to Dutch patients, Belgian patients reported significantly higher (more severe) pain (mean difference 7.3, 95% CI=0.1; 14.5), patients from the UK reported significantly higher nausea/vomiting (mean difference 8.6, 95% CI=1.8; 15.4) and Slovenian patients reported significantly lower (less severe) dyspnea (mean difference -15.8, 95% CI=-25.0; -6.5). Both Italian participants and participants from the UK reported significantly higher constipation than their Dutch counterparts (mean difference 8.8, 95% 0.4; 17.2 and 9.6, 95% CI=1.8; 17.3, respectively) (*Table 2*).

Country contrasts (*Table 3*) showed that the UK had a significantly higher (worse) mean score on fatigue and on dyspnea compared to the average mean scores of the other countries (fatigue: mean 46.7 vs. 36.3, $p = .04$, dyspnea: mean 33.1 vs. 21.2, $p < .01$). Slovenia had a significantly lower (better) mean score on dyspnea compared to the other countries' average mean score (mean 12.2 vs. 25.4, $p < .001$).

Patient-reported overall quality of life across countries

Figure 1 shows average overall QoL in the different countries. Compared to the Netherlands, all other studied countries but Denmark reported significantly lower (worse) overall QoL: Belgium (mean difference -8.4, 95% CI=-15.1; -1.7), Italy (mean difference -11.3, 95% CI=-18.4; -4.2), Slovenia (mean difference -13.1, 95% CI=-21.1; -5.2) and the UK (mean difference -9.4, 95% CI=-16.0; -2.9) (*Table 2*).

Country contrasts revealed a significantly higher (better) mean score on overall QoL for the Netherlands compared to the remaining other countries' average (mean 72.2 vs. 61.6, $p < .01$) (*Table 3*).

Table 1. Socio-demographic and clinical patient characteristics per country (N=1117)

	Total *N*=1117	**Belgium** *N*=207
Socio-demographic characteristics		
Age (years), mean (SD)	66.3 (9.8)	66.3 (9.4)
Years of education, mean (SD)	13.0 (4.6)	13.4 (4.8)
Gender, *n* (%), male	676 (60.5)	140 (67.6)
Marital status, *n* (%)		
Married, cohabiting	763 (69.3)	143 (70.4)
Divorced, separated	123 (11.2)	21 (10.3)
Widowed	120 (10.9)	21 (10.3)
Unmarried	95 (8.6)	18 (8.9)
Living with a partner, *n* (%), yes	800 (73.4)	157 (76.2)
Living conditions, *n* (%)		
Private household	1038 (94.7)	192 (95.5)
Institutionary care	7 (0.6)	3 (1.5)
Other	51 (4.7)	6 (3.0)
Having children, *n* (%), yes	959 (87.0)	175 (85.0)
Religion, *n* (%)		
Religious	548 (50.1)	109 (54.2)
Not religious	402 (36.7)	50 (24.9)
Prefer not to specify	144 (13.2)	42 (20.9)
Clinical characteristics		
Primary diagnosis		
Lung cancer stage III/IV	610 (54.6)	131 (63.3)
Colorectal cancer stage IV or metachronous metastases	507 (45.4)	76 (36.7)
Years since diagnosis, mean (SD)	1.5 (2.2)	1.5 (1.8)
Years since diagnosis of current cancer stage, mean (SD)	0.9 (1.2)	1.0 (1.3)
Current cancer treatment [a]		
Chemotherapy, *n* (%), yes	824 (74.1)	159 (77.2)
Targeted therapy, *n* (%), yes	145 (13.0)	52 (25.2)
Immunotherapy, *n* (%), yes	112 (10.1)	28 (13.6)
Radiation therapy, *n* (%), yes	84 (7.6)	11 (5.3)
Other, *n* (%), yes	155 (13.9)	13 (6.3)

Missing data: age *n*=3 (0.3%), years of education *n*=150 (13.4%), marital status *n*=16 (1.4%), living with a partner *n*=27 (2.4%), living conditions *n*=21 (1.9%), having children *n*=15 (1.3%), religion *n*=23 (2.1%), years since diagnosis *n*=4 (0.3%), years since diagnosis of current stage *n*=5 (0.4%), chemotherapy *n*=5 (0.4%), targeted therapy *n*=5 (0.4%), immunotherapy *n*=5 (0.4%), radiation therapy *n*=5 (0.4%), other *n*=5 (0.4%).

[a] Treatments were not mutually exclusive (multiple answers possible).

Denmark	**Italy**	**The Netherlands**	**Slovenia**	**United Kingdom**
N=136	*N*=170	*N*=252	*N*=97	*N*=255
66.3 (9.2)	64.9 (10.1)	65.2 (9.0)	66.2 (9.6)	68.3 (10.9)
13.5 (5.0)	11.4 (5.2)	13.4 (3.9)	11.6 (3.5)	13.6 (4.7)
73 (53.7)	107 (62.9)	164 (65.1)	61 (62.9)	131 (51.4)
94 (70.1)	115 (70.1)	187 (74.5)	56 (57.7)	168 (66.7)
10 (7.5)	21 (12.8)	27 (10.8)	10 (10.3)	34 (13.5)
19 (14.2)	14 (8.5)	19 (7.6)	13 (13.4)	34 (13.5)
11 (8.2)	14 (8.5)	18 (7.2)	18 (18.6)	16 (6.3)
101 (74.8)	121 (74.7)	191 (77.6)	59 (61.5)	171 (69.8)
124 (91.9)	160 (97.0)	242 (97.6)	96 (99.0)	224 (89.6)
0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.8)
11 (8.1)	5 (3.0)	4 (1.6)	1 (1.0)	24 (9.6)
124 (91.9)	143 (86.7)	222 (88.4)	79 (82.3)	216 (86.7)
39 (29.8)	115 (69.3)	110 (43.8)	55 (57.3)	120 (48.2)
75 (57.3)	29 (17.5)	113 (45.0)	33 (34.4)	102 (41.0)
17 (13.0)	22 (13.3)	28 (11.2)	8 (8.3)	27 (10.8)
75 (55.1)	80 (47.1)	118 (46.8)	63 (64.9)	143 (56.1)
61 (44.9)	90 (52.9)	134 (53.2)	34 (35.1)	112 (43.9)
1.5 (2.6)	1.8 (3.3)	1.8 (1.8)	1.1 (1.9)	1.3 (1.6)
1.0 (1.7)	0.7 (1.1)	1.2 (1.3)	0.6 (1.2)	0.6 (0.8)
128 (94.1)	148 (87.1)	146 (58.6)	58 (60.4)	185 (72.5)
29 (21.3)	39 (22.9)	21 (8.4)	0 (0.0)	4 (1.6)
1 (0.7)	15 (8.8)	60 (24.1)	0 (0.0)	8 (3.1)
1 (0.7)	5 (2.9)	24 (9.6)	32 (33.3)	11 (4.3)
1 (0.7)	3 (1.8)	48 (19.3)	28 (29.2)	62 (24.3)

Table 2. Functional impairment, symptom severity and overall quality of life by country (N = 1117). Significant differences are shown in bold.

	Emotional functioning	Physical functioning	Pain
	Mean (SD)	Mean (SD)	Mean (SD)
Total	77.1 (21.4)	81.9 (21.1)	20.9 (25.1)
	Mean difference [a] (95% CI)	Mean difference [a] (95% CI)	Mean difference [a] (95% CI)
Country of residence			
Belgium *(vs. the Netherlands)* [b]	**-7.5** **(-13.9; -1.1)**	-7.1 (-14.9; 0.7)	**7.3** **(0.1; 14.5)**
Denmark *(vs. the Netherlands)* [b]	3.9 (-2.9; 10.7)	-0.3 (-9.0; 8.4)	1.4 (-6.1; 8.9)
Italy *(vs. the Netherlands)* [b]	-2.4 (-9.1; 4.3)	-7.4 (-15.6; 0.9)	3.4 (-4.1; 11.0)
Slovenia *(vs. the Netherlands)* [b]	-2.9 (-10.4; 4.5)	-5.9 (-15.2; 3.5)	6.3 (-2.0; 14.7)
United Kingdom *(vs. the Netherlands)* [b]	-3.5 (-9.7; 2.7)	**-8.5** **(-16.2; -0.9)**	5.7 (-1.2; 12.7)
Socio-demographic and clinical patient characteristics retained in final models [c]			
Age (years)	**0.2** **(0.0; 0.4)** [c]	-0.2 (-0.3; 0.0) [d]	**-0.3** **(-0.5; -0.1)** [d]
Years of education	--------	**0.5** **(0.1; 0.9)** [d]	--------
Gender, female *(vs. male)*	**-4.1** **(-7.7; -0.6)**	**-4.2** **(-7.8; -0.7)**	--------
Primary diagnosis, colorectal cancer stage IV/ metachronous metastases *(vs. lung cancer stage III/IV)*	--------	--------	--------
Years since diagnosis of current cancer stage	--------	--------	--------
Current cancer treatment – targeted therapy, yes (*vs. no*)	--------	--------	--------

Missing data for independent variables: age *n*=3 (0.3%), years of education *n*=150 (13.4%), gender *n*=0 (0%), primary diagnosis *n*=0 (0%), years since diagnosis of current cancer stage *n*=5 (0.4%), current cancer treatment – targeted therapy *n*=5 (0.4%).

Missing data for dependent variables: emotional functioning *n*=10 (0.9%), physical functioning *n*=6 (0.5%), pain *n*=6 (0.5%), fatigue *n*=5 (0.4%), nausea/vomiting *n*=10 (0.9%), dyspnea *n*=11 (1.0%), insomnia *n*=10 (0.9%), appetite loss *n*=10 (0.9%), constipation *n*=12 (1.2%), overall quality of life *n*=21 (1.9%).

All outcome variables (0-100 scale) are measured by the EORTC QLQ-C15-PAL (emotional functioning: two extra items from the full EORTC QLQ-C30).

[a] For each of the outcome variables (functioning scales, symptom scales and overall quality of life)

Fatigue	Nausea/ vomiting	Dyspnea	Insomnia	Appetite loss	Constipation	Overall quality of life
Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
38.8 (26.2)	15.9 (24.4)	24.8 (28.1)	27.9 (28.9)	21.5 (30.0)	18.3 (27.9)	64.3 (21.3)
Mean difference [a] (95% CI)	Mean difference [a] (95% CI)	Mean difference [a] (95% CI)	Mean difference [a] (95% CI)	Mean difference [a] (95% CI)	Mean difference [a] (95% CI)	Mean difference [a] (95% CI)
1.4 (-6.2; 9.0)	5.8 (-1.2; 12.8)	3.1 (-4.9; 11.1)	7.0 (-1.5; 15.5)	4.2 (-5.6; 14.1)	2.3 (-5.8; 10.4)	**-8.4** **(-15.1; -1.7)**
-2.2 (-10.1; 5.8)	6.3 (-1.0; 13.5)	-0.9 (-9.1; 7.4)	8.5 (-0.2; 17.2)	-0.7 (-11.4; 10.1)	6.4 (-1.9; 14.7)	-5.7 (-13.0; 1.6)
0.8 (-7.2; 8.8)	-1.2 (-8.5; 6.1)	-2.1 (-10.4; 6.2)	8.0 (-0.8; 16.8)	-6.6 (-17.0; 3.8)	**8.8** **(0.4; 17.2)**	**-11.3** **(-18.4; -4.2)**
-5.1 (-14.0; 3.8)	1.1 (-6.9; 9.1)	**-15.8** **(-25.0; -6.5)**	5.2 (-4.5; 14.9)	3.8 (-7.9; 15.5)	3.0 (-6.3; 12.4)	**-13.1** **(-21.1; -5.2)**
6.4 (-1.1; 13.8)	**8.6** **(1.8; 15.4)**	7.0 (-0.6; 14.7)	7.1 (-1.0; 15.2)	8.2 (-1.5; 17.8)	**9.6** **(1.8; 17.3)**	**-9.4** **(-16.0; -2.9)**
--------	**-0.2** **(-0.4; 0.0)** [d]	--------	--------	--------	--------	--------
--------	--------	--------	--------	--------	--------	--------
7.4 **(3.2; 11.7)**	**6.2** **(2.1; 10.3)**	--------	--------	**7.0** **(2.1; 11.9)**	--------	**-4.3** **(-7.8; -0.9)**
--------	--------	**-11.8** **(-16.4; -7.2)**	-5.1 (-10.2; 0.1)	--------	**-9.0** **(-13.7; -4.3)**	--------
-1.5 **(-2.9; -0.4)** [d]	--------	--------	--------	--------	--------	--------
--------	--------	--------	**-10.3** **(-18.2; -2.4)**	--------	--------	**6.4** **(1.0; 11.8)**

[a] linear mixed model was fitted in order to estimate the differences in means of the outcomes for different countries. Country of residence was always part of the model as a fixed effect, centers (hospitals) was always considered a random effect. [b] Arbitrarily chosen reference group.

[c] For adjustment, potential predictive socio-demographic and clinical patient characteristics (cancer treatments, primary diagnosis, gender, age, years of education, living with a partner, having children, years since diagnosis, and years since diagnosis of the current stage) were evaluated using forward selection, resulting in a model for each outcome. Only socio-demographic and clinical variables retained in the final models are shown.

[d] Continuous variable: instead of diff. in means (95% CI), the reported coefficient indicates the mean increase (or decrease if negative) within a time-span of a year.

Table 3. Contrast testing for differences between individual country mean scores and the average mean of the remaining countries (N = 1117). Significant differences are shown in bold.

	Emotional functioning	**Physical functioning**	**Pain**	**Fatigue**
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Total	77.1 (21.4)	81.9 (21.1)	20.9 (25.1)	38.8 (26.2)
Country contrasts	Mean difference	Mean difference	Mean difference	Mean difference
Belgium vs. other	**73.3 vs. 78.0**	80.6 vs. 82.2	25.0 vs. 20.1	40.4 vs. 37.5
p-value [a]	**.04**	1.0	.59	1.0
Denmark vs. other	**81.6 vs. 76.3**	85.6 vs. 81.2	16.4 vs. 21.8	37.0 vs. 38.2
p-value [a]	**.04**	.47	1.0	1.0
Italy vs. other	76.3 vs. 77.4	81.1 vs. 82.1	18.7 vs. 21.4	36.5 vs. 38.3
p-value [a]	1.0	1.0	1.0	1.0
The Netherlands vs. other	79.2 vs. 76.8	87.6 vs. 80.8	18.3 vs. 21.5	34.2 vs. 38.8
p-value [a]	1.0	.26	.42	1.0
Slovenia vs. other	76.5 vs.77.3	80.1 vs. 82.3	25.1 vs. 20.1	33.3 vs. 39.0
p-value [a]	1.0	1.0	1.0	.29
United Kingdom vs. other	76.2 vs. 77.4	76.8 vs. 83.0	22.2 vs. 20.7	**46.7 vs. 36.3**
p-value [a]	1.0	.52	1.0	**.04**

Missing data for dependent variables: emotional functioning *n*=10 (0.9%), physical functioning *n*=6 (0.5%), pain *n*=6 (0.5%), fatigue *n*=5 (0.4%), nausea/vomiting *n*=10 (0.9%), dyspnea *n*=11 (1.0%), insomnia *n*=10 (0.9%), appetite loss *n*=10 (0.9%), constipation *n*=12 (1.2%), overall quality of life *n*=21 (1.9%).

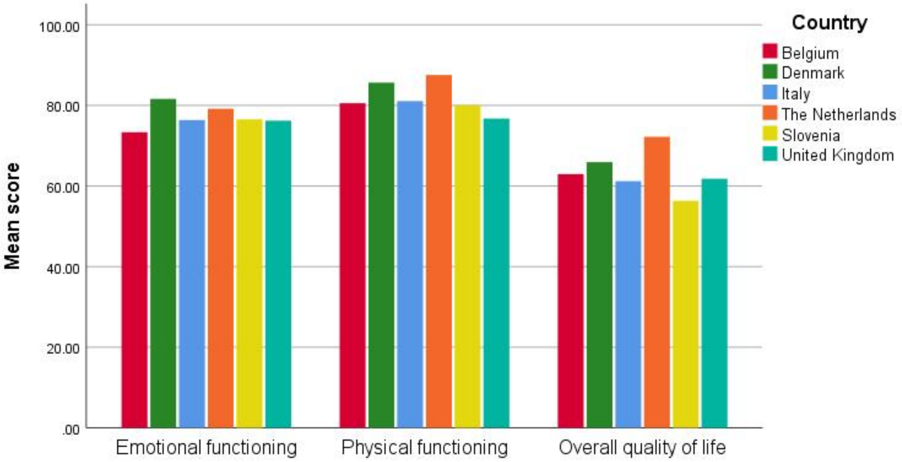

Figure 1. Average functional status and overall QoL in six European countries

Nausea/ vomiting	Dyspnea	Insomnia	Appetite loss	Constipation	Overall quality of life
Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
15.9 (24.4)	24.8 (28.1)	27.9 (28.9)	21.5 (30.0)	18.3 (27.9)	64.3 (21.3)
Mean difference	Mean difference	Mean difference	Mean difference	Mean difference	Mean difference
17.4 vs. 15.5	27.5 vs. 22.3	27.8 vs. 28.2	24.7 vs. 20.5	18.2 vs. 18.6	62.9 vs. 63.5
.66	.28	1.0	1.0	.86	.98
19.2 vs. 15.1	23.6 vs. 23.1	27.9 vs. 28.2	21.1 vs. 21.2	20.1 vs. 18.2	65.9 vs. 62.9
.66	1.0	1.0	1.0	1.0	.98
12.2 vs. 16.5	20.0 vs. 23.8	27.1 vs. 28.3	14.2 vs. 22.6	20.6 vs. 18.1	61.2 vs. 63.8
.19	1.0	1.0	.10	.66	.60
10.9 vs. 16.8	22.8 vs. 23.2	21.7 vs. 29.4	18.3 vs. 21.8	12.3 vs. 19.8	**72.2 vs. 61.6**
.44	1.0	.13	1.0	.26	**<.01**
14.4 vs. 16.1	**12.2 vs. 25.4**	30.9 vs. 27.5	21.6 vs. 21.1	17.9 vs. 18.6	56.3 vs. 64.8
.66	**<.001**	1.0	1.0	1.0	.23
20.8 vs. 14.8	**33.1 vs. 21.2**	33.2 vs. 27.1	27.2 vs. 20.0	22.0 vs. 17.8	61.8 vs. 63.7
.08	**<.01**	1.0	.11	.26	.98

All outcome variables (0-100 scale) are measured by the EORTC QLQ-C15-PAL (emotional functioning: two extra items on depression from the full EORTC QLQ-C30).

[a] *p*-values were adjusted using Shaffer's method to correct for multiple comparisons across contrasts.

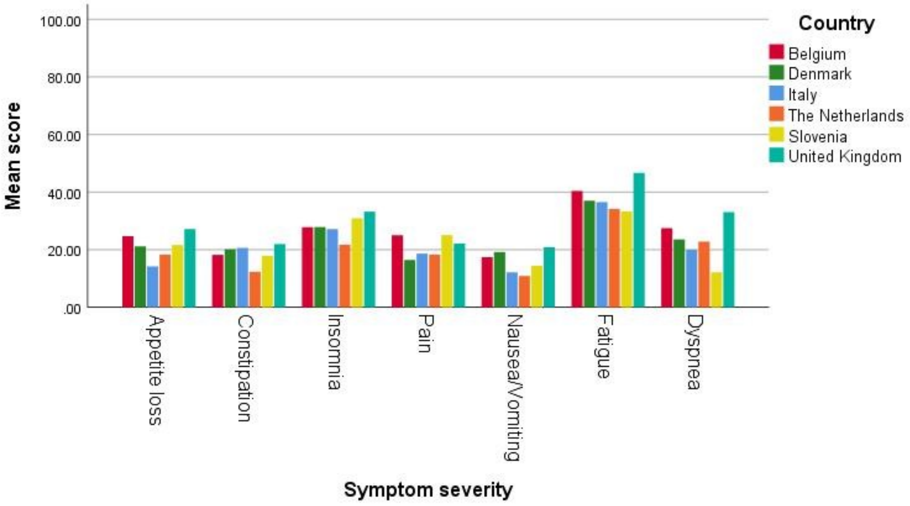

Figure 2. Average symptom severity in six European countries

2.4 DISCUSSION

Summary of findings

Self-reported emotional and physical functioning, symptom severity and overall QoL were assessed in a large international sample of patients with advanced stages of lung or colorectal cancer, and compared between six European countries. Cross-country comparisons revealed both similarities and differences across countries in these outcomes. For pain, nausea/vomiting and constipation, the differences in average scores between the highest and lowest scoring country were unlikely to be clinically significant (>10 points). The best scores (highest for EF and QoL, lowest for symptoms) were reported by Dutch and Danish patients. Belgian patients reported worse EF compared to the other countries averaged.

Interpretation of the results

Fatigue was the highest-scoring (most severe) self-reported symptom in this sample. This is not surprising, given that fatigue is generally recognized as one of the most prevalent and distressing symptoms of people with advanced cancer[1,31,32] that has been underreported and undertreated.[32] The severe nature of persistent fatigue has a major effect on QoL and limits people's participation in activities they enjoy.[32,33] Our results confirm that this is still an important area of attention in patients with advanced cancer. The second- and third-highest scoring symptoms in terms of severity overall were insomnia and dyspnea. Insomnia is often underrecognized among physicians and patients; if left untreated, insomnia can worsen other symptoms[34] and it has been related to adverse outcomes such as depression[35] and diminished QoL.[36] Dyspnea, too, severely interferes with a person's daily functioning and QoL.[37] This symptom is frequent in advanced cancer in general, but has the highest prevalence in patients with lung cancer and those approaching the end of life.[38]

We found several similarities in symptom severity across countries. For pain, nausea/vomiting and constipation, the difference in means between the highest and lowest scoring nation was smaller than 10 points, which is often used as a threshold for clinical relevance.[39] Despite the similarities, there were several noteworthy international differences in symptom severity, functioning and QoL. The most obvious finding to emerge from our data is that in general, the best scores (i.e., highest for EF and QoL, lowest for symptoms) appear to be reported by Dutch and Danish patients. The average score on overall QoL was significantly higher in the Netherlands (72.2) than in all other countries that participated in the study, except for Denmark (65.9). In Denmark, patients reported significantly better EF (81.6) compared to all other countries averaged, but this score was not significantly different from that of the Netherlands (79.2).

The comparatively better EF and QoL scores among patients from the Netherlands and Denmark are possibly a reflection of general high subjective wellbeing in these two countries. According to the most recent world happiness index report,[40] the Netherlands ranks as the sixth happiest country in the world, and Denmark – which has consistently ranked near the top in the past years – is at the second position. Similarly, a general population study has shown high average QoL among Dutch people (the Netherlands was the highest-scoring nation) and high average EF among Dutch and Danish people (the Netherlands was the highest-scoring nation, followed by Denmark).[41] Both countries are recognized for having a well-functioning and highly accessible healthcare system,[42,43] yet there are considerable differences between them regarding the integration of palliative care. Government policy in the Netherlands is based on the belief that palliative care is an integral component of the regular health system, rather than a distinct medical specialty as it is in several other countries. Palliative care is mainly provided as part of primary health care, with the general practitioner (GP) as the central figure and involvement of specialized palliative care services if necessary.[44] Such an approach might help in facilitating timely symptom detection as well as patient-clinician communication and/or shared decision-making earlier in the disease process. This interpretation seems rather unlikely in Denmark, where effective integration of palliative care into the healthcare system remains a major challenge. Danish GPs do not necessarily have a very active role in palliative care provision and specialist care is often only offered near the end of life.[45] Denmark does, however, have a tradition of extensive opioid prescription (fifth place in global opioid consumption ranking),[46] which has presumably contributed to the relatively low pain score in this country. Lower levels of physical discomfort may reduce stress and anxiety and contribute to higher EF.

In contrast, British patients regularly reported less favorable outcome scores. Compared to the Netherlands, the highest scoring nation overall, the UK had significantly lower average PF (NL: 87.6, UK: 76.8), higher (worse) nausea/vomiting (NL: 10.9, UK: 20.8) and higher constipation (NL: 12.3, UK: 22.0). Compared to all other countries averaged, the UK reported significantly worse average fatigue and dyspnea. This result is partly explained by the low dyspnea score in Slovenia, where one of the involved centers was an institution specialized in the diagnostics and treatment of patients with pulmonary diseases (University Clinic of Respiratory and Allergic Diseases, Golnik). Furthermore, the findings may reflect various kinds of inequality including socio-economic, quality and access to health care inequalities in the UK. Deprivation is probably a feature of the areas (North West and East Midlands) where the data were collected. These areas are relatively poor, for example compared to the South of England. It is also likely that there are lower levels of health literacy, possibly resulting in a delay in cancer diagnosis.[47] Moreover, the National Health Service (NHS) – an umbrella term for the publicly-funded healthcare systems of the UK – has been consistently underfunded during the last ten years. UK survival rates lag behind those of other European countries and health and cancer care spending in the UK appears to be lower than average among comparable countries.[48,49]

A recent study that collected European QLQ-C30 general population norm data and individual country norms for several European countries[41] gave roughly comparable results. In this study, the general population in the Netherlands – and Austria – also reported the best scores, i.e., highest for functioning and overall QoL and lowest for symptoms. The general population sample in the UK – and Poland – mostly reported worse scores. The authors mention a few possible reasons, which may apply to our results as well. They argue that because the EORTC QLQ-C30 underwent extensive linguistic validation and translation,[50] it is not likely that the country differences are explained by cultural variation in the meaning and interpretation of questionnaire items and/or response scales. A more plausible explanation seems to be that the findings reflect genuine differences between countries in people's self-reported health, which may be related to healthcare system or welfare state characteristics.[41] Since patients in our study received care as determined by the healthcare system in each country, we hypothesize that variations between countries in the availability, function and set up of (specialist) palliative care services, oncology care or treatment regimens may have contributed to the results. A comparative report on cancer in Europe (2019) has highlighted differences in health expenditure, efficiency in cancer care and access to (new) cancer medicines between European countries.[51] Our findings cannot provide direct evidence to support this hypothesis, because this particular study did not intend to measure and compare specific aspects of health systems among countries. Previous research has, however, confirmed the importance of national socio-economic factors in influencing the outcomes for cancer patients, such as cancer screening and survival, and has suggested that marked international disparities in cancer outcomes across Europe may be well due to different systems of health care, especially their funding for cancer management.[52,53]

Another remarkable finding of our study is that in Belgium, patients reported significantly worse EF (73.3) compared to the Netherlands (79.2) and compared to all other countries averaged. One possible explanation could lie in the fact that prevalence of mental illness in Belgian citizens in general has been shown to be among the highest in Europe.[54] The findings of our study indicate that the prevention and treatment of mental health issues remains challenging to the Belgian health system which need additional attention from healthcare providers, specifically in cancer care. In general, every hospital in Belgium with an oncology department has a multidisciplinary psychosocial team available for patients and family carers. Consultations with a psychosocial team are typically free of charge, but barriers such as a fear of stigmatization can limit the use of psychosocial support by patients who need it.[55]

Strengths and weaknesses

The major strength of this study is that it presents unique data of people with advanced stages of the two most common cancer types in six European countries with different healthcare systems. The design of the study and large international sample allowed us to perform a profound analysis of functioning, symptoms and QoL, considering detailed socio-demographic and clinical information. The study also has weaknesses. First, interpretation of the results is limited by the fact that the choice of a reference category is arbitrary in comparisons between countries. By also implementing an analysis comparing each country to the other countries' average score, we illustrated that the two approaches gave roughly similar results. Second, it is difficult to determine the etiology of symptoms, which could be from the illness, treatment(s) or both. A third limitation worth mentioning is that there is a possibility that patients with the worst levels of functioning were not included in the study; therefore, our results may underreport actual function, symptom burden and QoL deficits. Lastly, as the current study specifically addressed people with advanced lung and colorectal cancer, additional studies will be needed to establish generalizability by further exploring and replicating these outcomes with different (oncology) populations and environments.

Implications for research and practice

The results of this study underscore the important role of healthcare providers to recognize and consequently screen for the most burdensome physical and psychological symptoms in their efforts to support advanced cancer patients to control their symptoms and to remain engaged in daily life as much as possible. The findings also show that a one-size-fits-all policy should be avoided, because it is not sufficient to meet the challenges across nations which differ in the specific pain points they are experiencing. Future studies should investigate which specific features of the healthcare system (e.g., equitability of healthcare access), society, economy and culture people live in are most important in explaining cross-country differences in functioning, symptoms and QoL.

Conclusion

The optimization of functioning, symptom relief and overall QoL remain important objectives of every healthcare professional when taking care of patients with advanced cancer. There are similarities, but also substantial differences across countries in functional status, symptoms and overall QoL. Policy makers should take these differences into account and invest in offering health care catered to the needs of their population.

ADDITIONAL INFORMATION

Funding

This publication is based on the ACTION trial ('Advance care planning – an innovative palliative care intervention to improve quality of life in oncology'), a larger study about advance care planning in oncology conducted by a collaboration of research teams from the Netherlands, Denmark, Belgium, Slovenia, the UK, and Italy. The ACTION trial was funded by the European Union's Seventh Framework Programme for Research and Technological Development (FP7) (Proposal No. 6025410-2).

Conflicts of interest

The authors have no conflicts of interests to declare that are relevant to the content of this article.

Ethical approval

The ACTION trial was registered in the International Standard Randomised Controlled Trial Number (ISRCTN) registry (ISRCTN63110516) as of 10 March 2014. Ethical committee procedures were followed and approval was obtained in all countries and institutions involved.

Consent to participate

Patients who were deemed eligible by their care team and willing to consider possible participation were provided with more information about the study by the research team. Patients were given unrestricted time to consider participation and were informed that they were free to withdraw from participating in the study without any effect on their care. Prior to study enrollment, each participant in this study gave written informed consent to take part in the research.

Consent to publish

All study participants agreed to the use of their (anonymized) data as outlined in the information given to them prior to study start.

Authors' contributions

Mariëtte N. Verkissen, Aline De Vleminck, Mogens Groenvold, Lea J. Jabbarian, Judith A.C. Rietjens and Luc Deliens contributed to the study conception and design. Wilfried Cools, Mariëtte N. Verkissen and Aline De Vleminck contributed to the statistical analysis. The first draft of the manuscript was written by Mariëtte N. Verkissen and Aline De Vleminck. All authors contributed to the interpretation of the data and commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We thank all participating patients, hospital staff and the Advisory Board for their valuable contribution to this project.

We thank Bud Hammes and Linda Briggs for their advice throughout the project.

We gratefully acknowledge the ACTION consortium. Collaborators: Agnes van der Heide, Ida J. Korfage, Judith A.C. Rietjens, Lea J. Jabbarian, Suzanne Polinder, Pascalle F.A. Billekens, Johannes J.M. van Delden, Marijke C. Kars, Marieke Zwakman, Luc Deliens, Mariëtte N. Verkissen, Kim Eecloo, Isabel Vandenbogaerde, Kristof Faes, Kristian Pollock, Jane Seymour, Glenys Caswell, Andrew Wilcock, Louise Bramley, Sheila A. Payne, Nancy J. Preston, Lesley Dunleavy, Eleanor Sowerby, Guido Miccinesi, Francesco Bulli, Francesca Ingravallo, Giulia Carreras, Alessandro Toccafondi, Giuseppe Gorini, Urška Lunder, Branka Červ, Anja Simonič, Alenka Mimić, Hana Kodba-Čeh, Polona Ozbič, Mogens Groenvold, Caroline M. Arnfeldt Christensen, Anna Thit Johnsen.

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APPENDIX 1

Statistical methods

Statistical analyses were performed using R version 3.5.1 (2018-07-02). Linear mixed models were estimated in order to explore how each outcome (emotional functioning, physical functioning, symptoms and overall quality of life) could be understood in terms of the patients' country of residence, taking into account other socio-demographic and clinical patient characteristics. A few candidate predictor variables were left out of the analyses, because there was little variation in the observed values (living conditions), a considerable conceptual overlap between two predictor variables (marital status and living with a partner; we chose to use the latter) or a relatively large amount of missing information mainly corresponding to 'prefer not to specify' responses (religion). Given the present study's primary focus, country of residence was always considered part of the model as a fixed effect, along with the center (hospital), which was always considered a random effect. These variables were included in a stepwise selection procedure along with the other potential predictors: cancer treatments, primary diagnosis, gender, age, years of education, living with a partner, having children, years since diagnosis and years since diagnosis of the current cancer stage – in this order.

For each separate outcome, we started with a base model containing only centers (hospitals) and the key predictor of interest (country of residence) and then added the above-mentioned additional candidate variables one at a time. In each forward step, the candidate predictor under consideration was either retained or deleted from the model depending on its significance. Variables with doubtful results were initially removed and retried at the end of the modeling process. Variable selection decisions were based on Akaike's Information Criterion (AIC) to compare models and verified by applying likelihood ratio (LR) tests. The analysis continued until all potential predictors were evaluated resulting in a model for each of the outcome variables. The Netherlands (the country with the highest overall quality of life) was chosen as a reference category. No theoretical standard exists to determine which reference population is most 'appropriate', and the interpretation of the results can vary depending on which comparison group is chosen. To counter this concern, we implemented a second approach to analyzing the data to see whether the two parallel methods would lead to similar results. We conducted contrasts comparing each individual country's mean score to the average mean of the remaining countries, for all outcomes separately. We corrected for multiple testing across contrasts (i.e., controlled the experiment-wise error rate) by calculating adjusted p-values according to Shaffer's method.

APPENDIX 2

Appendix Table. Global overview of mean scores for functional impairment, symptom severity and overall quality of life per country (*N* = 1117)

	Emotional functioning	Physical functioning	Pain	Fatigue
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Total	77.1 (75.8; 78.3)	81.9 (80.7; 83.2)	20.9 (19.4; 22.3)	38.8 (37.3; 40.4)
Country of residence				
Belgium	73.3 (70.2; 76.5)	80.6 (77.3; 83.8)	25.0 (21.0; 29.0)	40.4 (36.6; 44.2)
Denmark	81.6 (78.4; 84.8)	85.6 (82.9; 88.4)	16.4 (12.6; 20.2)	37.0 (33.2; 40.9)
Italy	76.3 (73.4; 79.3)	81.1 (78.0; 84.1)	18.7 (14.8; 22.6)	36.5 (32.5; 40.5)
The Netherlands	79.2 (76.6; 81.7)	87.6 (85.4; 89.7)	18.3 (15.4; 21.2)	34.2 (31.0; 37.4)
Slovenia	76.5 (71.9; 81.2)	80.1 (76.0; 84.1)	25.1 (20.4; 29.7)	33.3 (28.6; 38.1)
United Kingdom	76.2 (73.5; 78.9)	76.8 (73.8; 79.7)	22.2 (19.1; 25.2)	46.7 (43.2; 50.1)

Missing data for dependent variables: emotional functioning *n*=10 (0.9%), physical functioning *n*=6 (0.5%), pain *n*=6 (0.5%), fatigue *n*=5 (0.4%), nausea/vomiting *n*=10 (0.9%), dyspnea *n*=11 (1.0%),

Nausea/ vomiting Mean (95% CI)	Dyspnea Mean (95% CI)	Insomnia Mean (95% CI)	Appetite loss Mean (95% CI)	Constipation Mean (95% CI)	Overall quality of life Mean (95% CI)
15.9 (14.4; 17.3)	24.8 (23.1; 26.4)	27.9 (26.1; 29.6)	21.5 (19.8; 23.3)	18.3 (16.7; 20.0)	64.3 (63.1; 65.6)
17.4 (13.8; 21.0)	27.5 (23.2; 31.7)	27.8 (23.7; 31.9)	24.7 (20.1; 29.2)	18.2 (14.1; 22.3)	62.9 (60.1; 65.7)
19.2 (15.1; 23.2)	23.6 (18.5; 28.6)	27.9 (23.2; 32.6)	21.1 (16.5; 25.8)	20.1 (15.4; 24.9)	65.9 (62.3; 69.6)
12.2 (9.0; 15.4)	20.0 (16.2; 23.7)	27.1 (22.8; 31.5)	14.2 (10.4; 18.0)	20.6 (16.4; 24.8)	61.2 (57.8; 64.6)
10.9 (8.3; 13.5)	22.8 (19.6; 26.0)	21.7 (18.6; 24.8)	18.3 (14.9; 21.7)	12.3 (9.5; 15.1)	72.2 (70.0; 74.4)
14.4 (9.6; 19.3)	12.2 (8.2; 16.1)	30.9 (26.3; 35.6)	21.6 (16.0; 27.3)	17.9 (12.6; 23.2)	56.3 (52.2; 60.5)
20.8 (17.4; 24.2)	33.1 (29.4; 36.7)	33.2 (29.1; 37.4)	27.2 (23.0; 31.4)	22.0 (18.1; 25.8)	61.8 (58.9; 64.7)

insomnia *n*=10 (0.9%), appetite loss *n*=10 (0.9%), constipation *n*=12 (1.2%), overall quality of life *n*=21 (1.9%). Mean scores are presented on a 0-100 scale.

3

Quality of life and symptom intensity over time in people with cancer receiving palliative care: results from the international European Palliative Care Cancer Symptom study

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This chapter is also published as an article in: *PLoS ONE* 2019; **14**(10): e0222988. [2019 SCI impact factor 2.740; journal ranking Q2; ranking n° 27 of 71 in MULTIDISCIPLINARY SCIENCES]

ABSTRACT

Background: People with advanced cancer experience multiple symptoms during their illness trajectory, which can fluctuate in intensity.

Aim: To describe the course of self-reported quality of life, emotional functioning, physical functioning and symptom intensity over time in cancer patients receiving palliative care.

Design: Longitudinal study with monthly assessments, using the EORTC QLQ-C15-PAL. Data were analysed (1) prospectively, from baseline to ≥8-month follow-up; and (2) retrospectively, by taking death as index date and comparing results from three cross-sectional subsamples at different stages of illness (time to death ≥6, 5-3 and 2-0 months). Linear mixed models were calculated.

Setting/participants: A total of 1739 patients (mean age 66, 50% male) from 30 palliative care centers in 12 countries were included.

Results: In prospective analyses, quality of life, functioning and symptoms – except nausea/vomiting – remained generally stable over time. In retrospective analyses, patients 2-0 months before death reported significantly lower quality of life and physical functioning scores than those 5-3 months before death, who in turn scored lower than those ≥6 months before death, suggesting progressive decline. Emotional functioning remained initially unchanged, but decreased in the last months. Pain, fatigue and appetite loss showed a stable increase in intensity towards death. Dyspnea, insomnia and constipation increased from 5-3 to 2-0 months before death. Nausea/vomiting only increased when comparing those ≥6 months before death with those 2-0 months before death.

Conclusion: While the prospective approach showed predominantly stable patterns for quality of life, functioning and symptom severity throughout study duration, retrospective analyses indicated that deterioration was already apparent before the terminal phase and accelerated close to death. Our findings support the importance of early symptom identification and treatment in this population, and highlight the need for further studies to explore what characterizes those with either lower or higher symptom burden at different time points towards death.

3.1 INTRODUCTION

Due to aging and more effective treatments, more people are living longer after being diagnosed with cancer, even those with progressive, incurable cancer. This may have detrimental effects on physical and emotional health.[1,2] Symptoms such as anxiety, depressed mood, pain, fatigue, dyspnea and appetite loss[3] can significantly impact quality of life and patients' ability to carry out daily activities.[4-6] Therefore, high-quality palliative cancer care requires optimal symptom management across the disease trajectory and towards the end of life, when patients with advanced cancer may experience worsening symptom burden and evident functional decline.[7-9]

Understanding how quality of life (QoL), emotional functioning (EF), physical functioning (PF) and symptoms progress over time is important, since it can help healthcare professionals working in palliative care achieve the best possible outcomes for patients at any point along the course of the advanced illness. However, although previous studies have described QoL, functioning and symptom burden in cancer patients in a palliative care setting, these studies were mostly cross-sectional or, if prospective, limited in follow-up. Describing changes in these variables over time requires the use of a design involving repeated registrations over an extended period of time.

In the present study, we first looked prospectively at a large international sample of people with cancer enrolled in palliative care, to address the following research questions:

1. How do QoL, EF and PF evolve over time?
2. How does the intensity of cancer-related symptoms evolve over time?

Secondly, we addressed these research questions retrospectively; therefore, we focused on those participants who had passed away during the study period, and examined whether QoL, functioning and symptoms differed significantly between three cross-sectional subsamples of deceased patients based on time to death (≥6, 5-3, and 2-0 months).

3.2 METHODS

Study design and setting

We used data from the multi-center longitudinal European Palliative Care Cancer Symptom (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. The participating centers were 24 hospital departments, four hospices, one nursing home, and one palliative home care service. Details of the study and participating centers can be found elsewhere.[10]

Study population

The study aimed to include a large number of palliative care cancer patients from different sites, with mixed cancer diagnoses and at various stages of their disease. Inclusion criteria 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: being treated with curative intent; inability to comply with study procedures due to psychiatric disorders; severe cognitive impairment or language problems; imminent death; or inability to come for follow-up due to medical, social, or geographical reasons.

Measurements

The data used in this paper were collected using a case report form on medical data completed by healthcare providers (HCP-CRF) and by participants' self-report on health and symptoms (patient-CRF). Both CRFs were completed monthly (3-5 weeks) for a minimum of three months, or until death or study withdrawal.

The HCP-CRF consisted of a brief set of medical and treatment-related variables, e.g., primary cancer diagnosis, comorbidities, anti-cancer treatment, and medication. A retrospective recording of date of death was performed in each study center in February 2014, approximately six months after the last study inclusion.

The patient-CRF consisted of key socio-demographic characteristics, e.g., age, gender, marital status, living situation and education (collected at baseline), and questions on quality of life (QoL) and symptom intensity. The variables of interest in our analysis were overall QoL, emotional functioning (EF), physical functioning (PF) and cancer-related symptoms as assessed by the palliative care version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C15-PAL).[11,12] The QLQ-C15-PAL consists of one item referring to overall QoL; an EF scale (four items: two extra items on depression from the full EORTC QLQ-C30 were added to the original two items); a PF scale (three items);

a pain scale (two items); a fatigue scale (two items); and five single items (nausea/vomiting, dyspnea, insomnia, appetite loss, constipation). Patients responded to a four-point Likert scale from 1 (not at all) to 4 (very much), except for the item on overall QoL, which was rated on a seven-point numerical scale from 1 (very poor) to 7 (excellent).

Scores and scale scores were calculated following the EORTC QLQ-C30 Scoring Manual[13] and its addendum.[14] After standardization by linear transformation, scores range from 0-100. Higher scores on overall QoL and the functioning scales represent higher QoL and higher levels of functioning. Higher symptom scores indicate more severe symptoms.

Data analysis

Statistical analyses were performed using IBM SPSS Statistics version 23.0. We handled missing data in the outcome variables according to the procedure outlined in the EORTC Scoring Manual.[13,14] If at least half of the items within a scale were completed, missing values were replaced with the average of the items that were present for the corresponding scale. If less than half of the items within a scale were answered, the scale score was defined as missing.

Linear mixed model (multilevel) analyses were conducted with repeated measures on patients nested in hospitals, and hospitals in countries. QoL, functioning and symptoms were the outcomes. Since assessments were completed at various (non-equidistant) time points, a time variable was included in each model (in months since baseline or months prior to death, depending on the analysis). Akaike's Information Criterion (AIC)[15] was used to select the most appropriate covariance structures to fit the data. All models included a random intercept and a random slope for time at the three levels.

For the prospective analysis, time points of patient assessments were rounded to the nearest whole month since baseline. Estimated mean scores for QoL, EF, PF and symptoms with 95% confidence intervals were calculated for each month. Because of small numbers of observations, months 8-14 were combined (≥8). Linear mixed models as described above were used to test whether mean scores for the different time points differed significantly from the baseline value. Bonferroni-Holm adjustment was applied to correct for the problem of multiple comparisons. Mann-Kendal tests were used to detect consistently increasing or decreasing (monotonic) trends.

For the retrospective analysis, we used death as index date. Time points of patient assessments were rounded to the nearest whole month prior to death. Estimated mean scores and 95% confidence intervals were calculated for three cross-sectional subsamples which were constructed based on time to death, namely ≥6 (group 1), 5-3 (group 2), and 2-0 months (group 3). Statistical differences in mean scores were evaluated between the three groups.

All analyses were two-tailed and *p*-values smaller than 0.05 were considered statistically significant. In those cases where Bonferroni-Holm adjusted *p*-values were calculated (prospective analysis), the experiment-wise error rate (EER) was set at 5%.

Ethical considerations

The study was performed according to the Declaration of Helsinki and was registered in the ClinicalTrial.gov database (no. NCT01362816). Ethical approval was obtained at each site and all participants gave written informed consent prior to study start. The ethics committees/institutional review boards of following centers gave ethical approval for the study: Southern Adelaide Palliative Services, Adelaide, South Australia (Australia); Ghent University Hospital, Ghent (Belgium); Comprehensive Cancer Centre, Vratsa (Bulgaria); Cross Cancer Institute, Northern Alberta (Canada); The Edmonton Zone Palliative Care Program, Alberta (Canada); Rigshospitalet, Copenhagen (Denmark); Bispebjerg Hospital, Copenhagen (Denmark); Cancer Prevention Center (CPC), Tbilisi (Georgia); Fondazione IRCCS Istituto Nazionale dei Tumori, Milan (Italy); Hospital of Piacenza, Piacenza (Italy); Hospice Villa Speranza, Rome (Italy); Istituti Clinici di Perfezionamento Hospital, Milan (Italy); U.O. Complessa di Cure Palliative e Terapia del Dolore, Istituti Clinici di Perfezionamento Hospital, Milan (Italy); University of L'Aquila, L'Aquila (Italy); Arcispedale Santa Maria Nuova, Reggio Emilia (Italy); St. Olavs University Hospital, Trondheim (Norway); Oslo University Hospital, Oslo (Norway); Haraldsplass Deaconess Hospital, Bergen (Norway); Øya Community Hospital, Trondheim (Norway); Instituto Português de Oncologia Francisco Gentil, Lisbon (Portugal); Hospital Universitário Arnau de Vilanova, Lleida (Spain); Clínica Universidad de Navarra, Pamplona (Spain); Hospital Centro de Cuidados Laguna, Madrid (Spain); Institut Catala D'Oncologia, Barcelona (Spain); Cantonal Hospital, St. Gallen (Switzerland); Kantonsspital Graubünden, Chur (Switzerland); St Gemma's Hospice, Leeds (United Kingdom); West Lothian Community Specialist Palliative Care Team, Edinburgh (United Kingdom); Nottingham University Hospitals NHS Trust, Nottingham (United Kingdom); Marie Curie Cancer Care Hospice, Glasgow (United Kingdom).

3.3. RESULTS

Characteristics of the study population

The baseline sample consisted of 1739 people from 12 different countries. At study entry participants had a mean age of 65.9 years (SD = 12.4), and there was an even gender distribution (*Table 1*). The predominant diagnoses were cancer of the digestive (30.4%) and respiratory organs (19.8%) and breast cancer (16.5%). At inclusion, 41.4% were receiving chemotherapy, while 40.6% were not receiving any treatment. Most people were included at hospital palliative care units (46%) and general oncology departments (34.5%).

Of the total sample, 1090 (62.7%) people were reported dead during the follow-up period. A confirmed date of death was not available for 27 participants; survival length for the 1063 people with a verified date of death is categorized in *Table 1* and shows that around 68% died within six months from inclusion.

Prospective analysis: quality of life and symptom intensity over time

The sample decreased from 1739 participants at baseline to 1138 (65.4%) at month 1, 857 (49.3%) at month 2, 632 (36.3%) at month 3, 452 (26%) at month 4, 378 (21.7%) at month 5, 255 (14.7%) at month 6, 66 (3.8%) at month 7, and 42 (2.4%) at month ≥8; thus, three-quarters of the sample had dropped out at month 4 (*Figure 1*).

At inclusion (baseline), patients' EORTC QLQ-C15-PAL estimated mean scores were 51.18 for overall quality of life (QoL), 65.45 for emotional functioning (EF) and 61.77 for physical functioning (PF). No significant differences between baseline and subsequent QoL, EF and PF mean scores were found (*Table 2*). Participants' mean score for pain was significantly lower, indicating less pain, at month 1 (37.33) compared with baseline (41.88); pain mean scores at the other months were not significantly different from the baseline score (*Table 2*). Mean scores for nausea/vomiting were significantly lower compared with baseline (20.06) at month 4 (15.09), 5 (12.81), 6 (13.65), 7 (13.02) and ≥8 (12.68), suggesting a downward trend which was confirmed by a Mann-Kendal trend test ($p<.001$) (not shown in table). For insomnia, participants scored significantly lower than baseline (33.25) at month 2 (27.91), 3 (27.57) and 4 (26.26). Estimated mean scores for appetite loss were significantly lower than baseline (36.89) at month 3 (30.03) and 5 (29.64). Constipation mean scores were lower at month 3 (21.81) and 4 (21.64) compared to baseline (28.56). Mann-Kendal tests did, however, not reveal statistically significant trends for these symptoms. For dyspnea (baseline mean score 27.17) and fatigue (baseline mean score 52.20), there were no significant differences with baseline at any time point.

Table 1. Patient characteristics

Socio-demographic characteristics at baseline (*n* patients = 1739)		Missing, *n* (%)
Age, mean ± SD	65.9 ± 12.4	1 (0.1)
Gender, *n* (%)		3 (0.2)
Male	865 (49.8)	
Female	871 (50.2)	
Country, *n* (%)		0 (0.0)
Australia, 1 site (AU)	35 (2.0)	
Belgium, 1 site (WE)	101 (5.8)	
Bulgaria, 1 site (EE)	31 (1.8)	
Canada, 2 sites (AM)	94 (5.4)	
Denmark, 2 sites (NE)	104 (6.0)	
Georgia, 1 site (EE)	19 (1.1)	
Italy, 7 sites (SE)	605 (34.8)	
Norway, 4 sites (NE)	249 (14.3)	
Portugal, 1 site (SE)	62 (3.6)	
Spain, 4 sites (SE)	233 (13.4)	
Switzerland, 2 sites (CE)	72 (4.1)	
United Kingdom, 4 sites (WE)	134 (7.7)	
Clinical characteristics at baseline (*n* patients = 1739)		Missing, *n* (%)
Primary cancer diagnosis, *n* (%)		0 (0.0)
Digestive organs	528 (30.4)	
Respiratory organs	345 (19.8)	
Breast	287 (16.5)	
Male genital organs	129 (7.4)	
Gynaecological	103 (5.9)	
Urinary	79 (4.5)	
Leukaemia or lymphoma	47 (2.7)	
Head	61 (3.5)	
Other	160 (9.2)	
Comorbidity (numbers), *n* (%)		15 (0.9)
0	698 (40.5)	
1	646 (37.5)	
2	287 (16.6)	
≥3	93 (5.4)	
Current oncology treatment: yes, *n* (%)		
Chemotherapy	715 (41.4)	13 (0.7)
Radiotherapy	89 (5.2)	14 (0.8)
Hormonal treatment	175 (10.1)	14 (0.8)

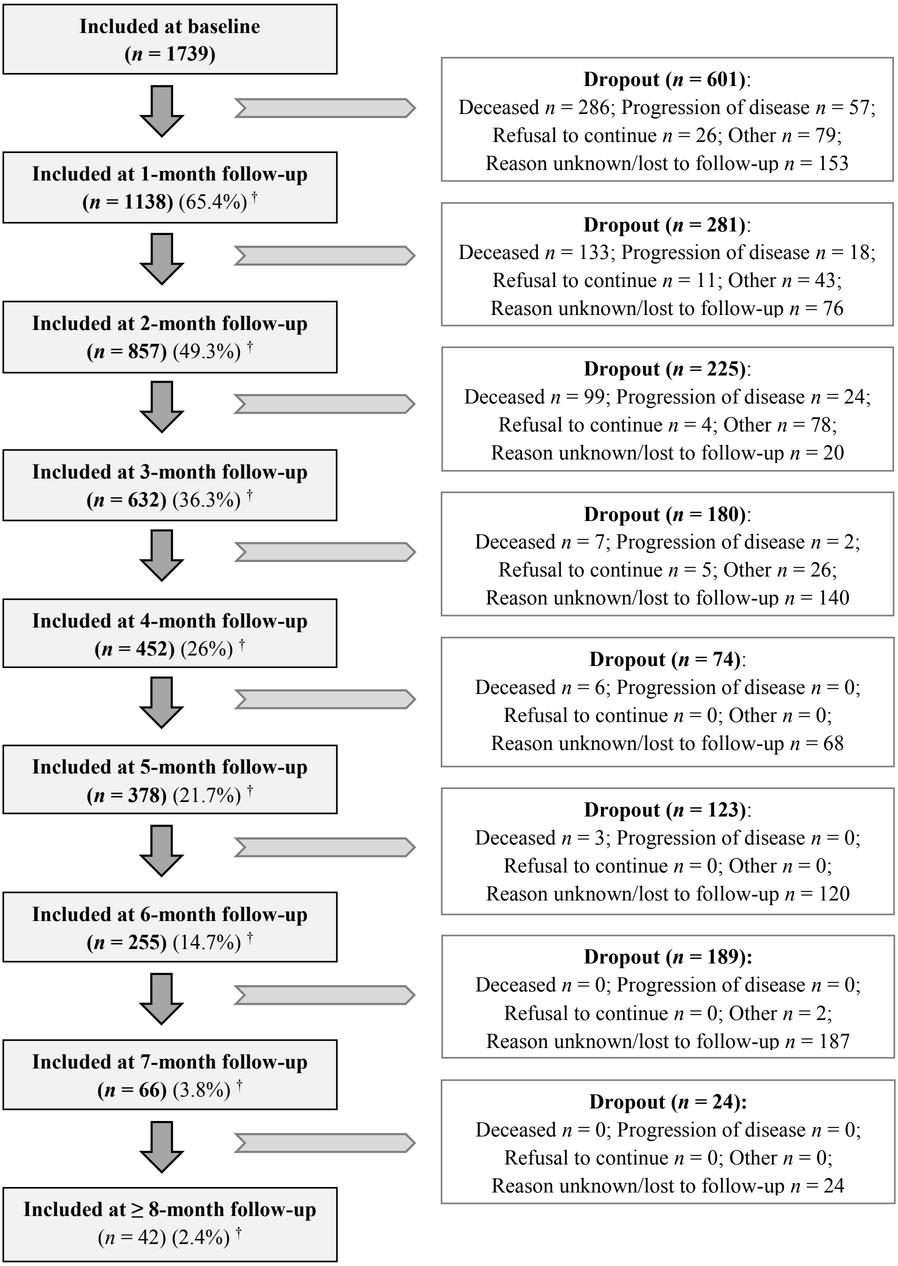
Table 1. Continued

Socio-demographic characteristics at baseline (*n* patients = 1739)		Missing, *n* (%)
Age, mean ± SD	65.9 ± 12.4	1 (0.1)
Other treatment	97 (5.6)	14 (0.8)
No treatment	700 (40.6)	13 (0.7)
Current medication: yes, *n* (%)		
Opioids	1012 (59.3)	33 (1.9)
Non-opioid analgesics	808 (47.4)	35 (2.0)
Corticosteroids	782 (45.8)	30 (1.7)
Laxatives	828 (48.6)	34 (2.0)
Antiemetics	681 (40.2)	43 (2.5)
Sedatives/anxiolytics	526 (30.9)	37 (2.1)
Antidepressants	281 (16.5)	37 (2.1)
Treatment setting, *n* (%)		48 (2.8)
Inpatients	365 (21.6)	
Outpatients (day care)	1026 (60.7)	
Home care	300 (17.7)	
Place of care, *n* (%)		25 (1.4)
Oncology department	592 (34.5)	
Hospital palliative care unit	788 (46.0)	
Other hospital department	20 (1.2)	
Hospice	144 (8.4)	
Nursing home	15 (0.9)	
Primary care setting/home	155 (9.0)	
Survival (*n* patients = 1739)		
Still alive at the end of the study period, or survival status unknown, *n* (%)	649 (37.3)	
Deceased during follow-up, *n* (%)	1090 (62.7)	
Verified date of death (*n* patients = 1063)*		
Survival in days from inclusion, *n* (%)		
<30 days	161 (15.1)	
30-89 days	309 (29.1)	
90-149 days	187 (17.6)	
150-180 days	67 (6.3)	
>180 days	339 (31.8)	

Abbreviations: SD, standard deviation; AU, Australia; WE, Western Europe; EE, Eastern Europe; AM, America; NE, Northern Europe; SE, Southern Europe; ME, Middle Europe.

Percentages may not sum to 100 due to rounding.

* A date of death was not registered for 27 out of 1090 patients that were reported dead during follow-up.



† Assessments were rounded to the nearest whole month post-baseline.

Figure 1. Flow diagram of participants throughout the course of the study

Retrospective analysis: quality of life and symptom intensity over time towards death

Table 3 shows estimated mean scores for QoL, EF and PF obtained from three cross-sectional subsamples at different stages of illness (time before death, group 1: ≥6 months, group 2: 5-3 months, group 3: 2-0 months). For QoL and PF, mean scores of participants 2-0 months prior to death (group 3) were significantly lower than mean scores of those 5-3 months prior to death (group 2), and mean scores of the latter group were significantly lower than mean scores of those ≥6 months prior to death (group 1). This suggests that QoL and PF worsened throughout the disease trajectory towards death. For EF, a significant decline was only found when comparing those 5-3 months prior to death (group 2) with those 2-0 months prior to death (group 3). *Figure 2* shows QoL, EF and PF for the different subsamples.

Participants 2-0 months prior to death (group 3) were found to have significantly higher mean scores for pain, fatigue and appetite loss than those 5-3 months prior to death (group 2), and those from the latter group were found to have significantly higher mean scores than those ≥6 months prior to death (group 1), indicating an increase in intensity, thus deterioration, of these symptoms over time towards death (*Table 3*). For dyspnea, insomnia and constipation, a significant deterioration was only found when comparing the mean scores of those 5-3 months prior to death (group 2) with the mean scores of those 2-0 months prior to death (group 3), and for nausea/vomiting only when comparing those ≥6 months prior to death (group 1) with those 2-0 months prior to death (group 3).

Table 2. Prospective analysis: quality of life and symptom intensity over time as assessed by the EORTC QLQ-C15-PAL in people with cancer receiving palliative care

	Baseline (*Ref*) (*n* patients = 1739) †	**Month 1** (*n* patients = 1138) †	**Month 2** (*n* patients = 857) †	**Month 3** (*n* patients = 632) †
	Estimated mean (95% CI)	Estimated mean (95% CI)	Estimated mean (95% CI)	Estimated mean (95% CI)
Overall QoL ±	51.18 (47.09;55.26)	52.25 (48.07;56.43)	53.81 (49.55;58.08)	52.30 (47.93;56.66)
Emotional functioning ±	65.45 (57.34;73.57)	66.70 (58.56;74.84)	67.35 (59.18;75.52)	67.11 (58.92;75.30)
Physical functioning ±	61.77 (54.06;69.48)	59.36 (51.59;67.14)	59.90 (52.05;67.75)	56.61 (48.72;64.49)
Symptoms ±				
Pain	41.88 (36.87;46.90)	**37.33**[*] (32.23;42.42)	37.62 (32.44;42.80)	38.96 (33.71;44.20)
Fatigue	52.20 (45.50;58.89)	51.72 (44.99;58.46)	49.38 (42.60;56.17)	51.16 (44.33;57.99)
Nausea/vomiting	20.06 (15.13;24.99)	20.05 (15.08;25.02)	18.24 (13.22;23.26)	16.86 (11.81;21.91)
Dyspnea	27.17 (20.65;33.69)	28.44 (21.87;35.01)	26.87 (20.24;33.50)	30.86 (24.19;37.54)
Insomnia	33.25 (28.24;38.25)	29.61 (24.56;34.66)	**27.91**[**] (22.78;33.04)	**27.57**[**] (22.37;32.77)
Appetite loss	36.89 (31.31;42.46)	33.58 (27.94;39.23)	32.23 (26.48;37.99)	**30.03**[**] (24.19;35.87)
Constipation	28.56 (25.80;31.33)	25.49 (22.57;28.41)	25.58 (22.52;28.65)	**21.81**[**] (18.56;25.06)

Abbrevations: QoL, quality of life; CI, confidence interval.

§ Linear mixed models were analyzed with repeated measures on patients nested in hospitals, and hospitals in countries.

Bonferroni-Holm adjustment was applied to all pairwise comparisons.

± Scores were linearly converted into a 0-100 scale according to the EORTC guidelines, with higher values representing better quality of life, better functioning and higher symptom severity.

Time [§]				
Month 4 (*n* patients = 452) [†]	**Month 5** (*n* patients = 378) [†]	**Month 6** (*n* patients = 255) [†]	**Month 7** (*n* patients = 66) [†]	**Month ≥8** (*n* patients = 42) [†]
Estimated mean (95% CI)	Estimated mean (95% CI)	Estimated mean (95% CI)	Estimated mean (95% CI)	Estimated mean (95% CI)
53.09 (48.50;57.68)	52.69 (47.99;57.39)	51.11 (46.15;56.08)	51.46 (45.59;57.34)	49.80 (43.42;56.19)
67.48 (59.24;75.72)	67.97 (59.71;76.24)	66.59 (58.24;74.95)	69.03 (60.37;77.69)	65.17 (56.26;74.09)
59.41 (51.41;67.41)	58.82 (50.73;66.90)	57.87 (49.57;66.17)	61.68 (52.97;70.40)	58.45 (49.14;67.76)
37.60 (32.16;43.03)	40.63 (35.09;46.18)	39.54 (33.69;45.40)	36.24 (29.60;42.88)	43.31 (35.96;50.66)
50.28 (43.35;57.22)	49.77 (42.77;56.78)	52.19 (45.01;59.38)	51.41 (43.65;59.17)	52.28 (44.00;60.57)
15.09[**] (9.99;20.18)	**12.81**[**] (7.71;17.91)	**13.65**[**] (8.45;18.85)	**13.02**[**] (7.41;18.62)	**12.68**[*] (6.53;18.82)
27.58 (20.79;34.36)	28.31 (21.47;35.14)	29.20 (22.19;36.21)	31.17 (23.59;38.75)	29.86 (21.68;38.03)
26.26[**] (20.87;31.65)	28.37 (22.88;33.86)	28.58 (22.78;34.37)	31.90 (25.02;38.78)	25.60 (17.95;33.24)
32.30 (26.22;38.37)	**29.64**[*] (23.46;35.83)	33.37 (26.84;39.90)	33.73 (26.07;41.38)	33.17 (24.46;41.87)
21.64[**] (17.96;25.31)	23.54 (19.64;27.43)	23.30 (18.93;27.67)	24.80 (18.89;30.70)	28.07 (21.30;34.83)

[**] Estimated mean score differed significantly from baseline value using an experiment-wise error rate (EER) of 0.01.

[*] Estimated mean score differed significantly from baseline value using an experiment-wise error rate (EER) of 0.05.

[†] ≥1 assessment per patient possible because assessments were rounded to the nearest whole month.

Table 3. Retrospective analysis: quality of life and symptom intensity over time towards death

	Time to death (in months) [§]		
	Period 1 (≥6) (*n* patients = 369) [†]	**Period 2 (5-3)** (*n* patients = 442) [†]	**Period 3 (2-0)** (*n* patients = 675) [†]
	Estimated mean (95% CI)	Estimated mean (95% CI)	Estimated mean (95% CI)
Overall QoL [±]	57.62 (53.32;61.92)	51.44 (47.19;55.68)	43.83 (39.60;48.07)
Emotional functioning [±]	73.74 (68.45;79.03)	71.49 (66.25;76.72)	66.49 (61.27;71.72)
Physical functioning [±]	67.73 (62.11;73.34)	61.20 (55.71;66.70)	49.82 (44.35;55.29)
Symptoms [±]			
Pain	33.77 (29.28;38.26)	39.94 (35.49;44.39)	45.72 (41.28;50.16)
Fatigue	43.54 (38.62;48.46)	50.42 (45.56;55.28)	59.80 (54.95;64.65)
Nausea/vomiting	14.93 (10.61;19.25)	17.10 (12.88;21.32)	19.61 (15.44;23.78)
Dyspnea	24.49 (18.27;30.71)	27.05 (20.90;33.20)	33.72 (27.59;39.85)
Insomnia	25.38 (20.39;30.37)	25.63 (20.73;30.52)	31.57 (26.71;36.43)
Appetite loss	26.89 (21.63;32.15)	34.76 (29.60;39.91)	43.94 (38.80;49.07)
Constipation	25.33 (21.17;29.48)	26.08 (22.04;30.13)	30.86 (26.80;34.92)

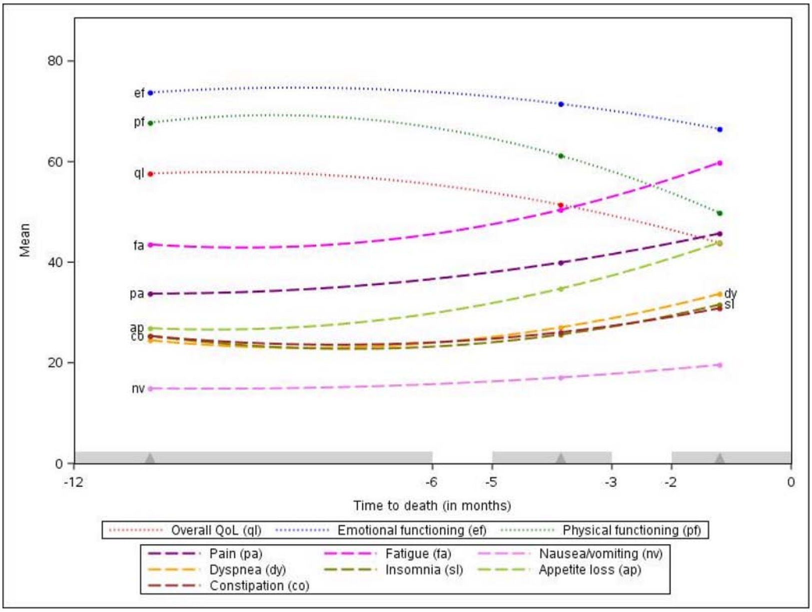
Abbrevations: QoL, quality of life CI, confidence interval.

[§] Linear mixed model analyses were performed with repeated measures on patients nested in hospitals, and hospitals in countries.

Δ Period 2 and period 1	Δ Period 3 and period 2	Δ Period 3 and period 1
Mean difference (*p*-value)	Mean difference (*p*-value)	Mean difference (*p*-value)
-6 (<.001)	**-8** (<.001)	**-14** (<.001)
-2 (.078)	**-5** (<.001)	**-7** (<.001)
-7 (.005)	**-11** (<.001)	**-18** (<.001)
+6 (.002)	**+6** (.003)	**+12** (<.001)
+7 (<.001)	**+9** (<.001)	**+16** (<.001)
+2 (.247)	+3 (.156)	**+5** (.016)
+3 (.085)	**+7** (<.001)	**+9** (<.001)
+0 (.901)	**+6** (.002)	**+6** (.003)
+8 (<.001)	**+9** (<.001)	**+17** (<.001)
+1 (.593)	**+5** (.001)	**+6** (.001)

[±] Scores were linearly converted into a 0-100 scale according to the EORTC guidelines, with higher values representing better quality of life, better functioning and higher symptom intensity.

[†] ≥1 assessment per patient possible.



Mean scores are depicted for each subsample: ≥6 months prior to death: 10.73; 5-3 months prior to death: 3.9; 0-2 months prior to death: 1.2.

Dotted lines: higher mean scores indicate a higher average QoL or higher level of functioning.

Dashed lines: higher mean scores indicate higher average symptom severity.

Figure 2. Retrospective analysis: quality of life and symptom intensity over time towards death

3.4 DISCUSSION

Main findings

To our knowledge, this is the first multi-center study to evaluate changes in self-reported quality of life (QoL), emotional functioning (EF), physical functioning (PF), and symptoms (pain, fatigue, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation) over time in a large international sample of people with advanced cancer receiving palliative care. A prospective analysis of the entire study sample showed general stability for QoL, EF, PF and symptoms from baseline throughout the study period (≥8-month follow-up). A retrospective analysis of participants who had passed away during follow-up revealed a significant deterioration towards death for QoL, PF, pain, fatigue and appetite loss when comparing cross-sectional subsamples of patients ≥6 months prior to death with those 5-3 months prior to death, and those 5-3 months prior to death with 2-0 months prior to death. EF, dyspnea, insomnia and constipation only showed significant deterioration when comparing those 5-3 months prior to death with those 2-0 months prior to death.

A possible explanation for the consistency of QoL, EF, PF and symptom intensity over time in the prospective analysis is that cancer in general tends to follow a trajectory of a long period of clinical stability. This reflects the well-known trajectory representing the typical course of cancer proposed by Lynn and Adamson (2003)[9] according to which individuals often maintain comfort and relatively normal functioning for a substantial time, and only show a rapid decline in the final weeks before death. Moreover, intensification of palliative care to alleviate suffering and enhance comfort may have prevented further deterioration of QoL and slowed or stabilized symptom progression over time.

The prospective finding that QoL, functioning and symptoms were stable over time did not exclude the possibility of symptoms to get worse or become harder to control as death approaches (i.e., the typical period of evident decline near the end of life as described by Lynn and Adamson), because this analysis also included patients who were still alive at the end of the follow-up period. Our retrospective analysis revealed a different picture, suggesting that deterioration in QoL, PF and three prominent symptoms (pain, fatigue, appetite loss) did not only occur at the end of life (in the terminal phase), but became noticeable already relatively early, around 5-3 months before death.

A striking finding was that EF did not significantly decrease when comparing those ≥6 months prior to death with those 5-3 months prior to death but did seem to deteriorate substantially in the last few months (i.e., when comparing those 5-3 months prior to death with those 2-0 months prior to death). It is possible that patients experience a coping shift or a delayed emotional response to acknowledging the physical changes or challenges that are likely to become more pronounced as the disease progresses, such as reduced energy and poor appetite. It could also have been a result of the increasing number of stressful circumstances that may be experienced by individuals who are facing death in the near future (e.g., uncertainty, numerous losses and adjustments, anticipatory grief).[16] However, emotional changes may occur at different times and intensities throughout the disease trajectory, and cancer patients in palliative care are known to be a vulnerable population at risk of mental health problems including anxiety and depressive symptoms.[17-19] Since psychological distress in cancer patients may lead to adverse outcomes such as poorer QoL and survival, timely recognition and management of distress is essential.

Comparing our results directly to data from other studies is difficult because of the wide variety of population characteristics, data collection methods and instruments used across studies. Our findings are, however, generally consistent with available evidence suggesting that QoL, functioning and symptom distress change at different rates at different points in time, and that decline tends to spiral downwards more rapidly in the last months or weeks of life ('terminal drop').[20-26] Additionally, it is interesting to note that pain, fatigue and appetite loss not only were the three symptoms starting to deteriorate most early, but were also the most severe symptoms (i.e., highest mean scores) in all three different periods of time before death. This finding is not completely unexpected, since it is known from previous research that pain, fatigue and appetite loss are among the most debilitating and commonly reported symptoms in advanced cancer.[3,27-30] Nausea/vomiting was relatively the least severe symptom, a result that is consistent with previous research showing that nausea and vomiting are generally less bothersome and less frequently occurring symptoms in patients with advanced disease than other symptoms such as pain, fatigue and dyspnea,[31] also in palliative care populations.[20,32,33]

Strengths and limitations

The EPCCS study is the largest international, longitudinal study in a palliative care cancer population of which we are aware. Strengths of this research include the prospective design, the sample size and the inclusion of patients from multiple centres, which made it possible to follow QoL, EF, PF and symptoms over an extended period of time, in a considerable number of vulnerable people in Europe and beyond. The linear mixed model procedure adopted in this study is a powerful approach as it takes account of repeated measurement and clustering effects at both hospital and country level. Despite these strengths, our study also has limitations which need to be acknowledged. The first concerns the representativeness of the sample. The EPCCS study's main report[10] showed that there is large variation in the organization and delivery of palliative care services and in patient characteristics (e.g., primary tumor sites, stages and treatment regimens) across Europe. Clear population criteria will be essential in future research to facilitate the comparison of results across different studies and countries.[10] A second notable issue is that data were relatively sparse in the last months of the study.

Patient attrition is an inherent difficulty of longitudinal studies, especially in palliative care where drop out due to deterioration or death is very likely. Third, it is possible that participants with the worst levels of functioning were not included in the study, which may have resulted in an underestimation of the QoL and symptom experience.

Implications for research and practice

The findings of our study indicate that optimization of QoL, functioning and symptom relief remain challenges to healthcare providers involved in palliative cancer care and becomes more difficult to achieve as the illness progresses towards death. There is a need for systematic and standardised screening of QoL, functioning and physical as well as psychological symptoms to become an integral part of clinical routine during the disease trajectory. This could help determine when palliative care needs to be strengthened and guide the care for these individuals, which is important since physicians tend to underestimate the severity of symptoms.[34] Moreover, routine standardised self-report of symptoms may improve patient-physician communication.[35] Additional studies should investigate which strategies of screening are most effective.[36]

The present study was explorative in nature and did not assess factors associated with QoL, functioning and symptoms over time. It would be interesting for future research to investigate what characterizes patients with different levels of symptomatology (e.g., low, medium, high) at different time points before death. From a clinical point of view, it might be valuable to distinguish between symptoms that are less or more difficult to control by medication as death comes closer.

Conclusions

A prospective analysis of a large international sample of palliative care cancer patients showed that self-reported QoL, functioning and cancer-related symptoms remained stable from inclusion (baseline) over time throughout the study duration, where a retrospective analysis revealed that, although deterioration accelerated as death approached, this was already apparent before the terminal phase. Our findings further support the importance of early symptom detection and treatment in this population, and the need for future research to look at characteristics of patients with lower or higher symptom burden at different time points towards death.

ADDITIONAL INFORMATION

Declaration of conflicting interests

None of the authors have declared any potential conflict of interest with respect to the research, authorship, and/or publication of this article.

Authorship

All contributing authors meet the criteria for authorship. M.J.H., S.V.B., S.K., L.D. and K.P. contributed to the study concept, design and data acquisition. M.N.V. and K.P. contributed to the statistical analysis. M.N.V. drafted the manuscript with input from all authors. All authors contributed to the interpretation of the results and approved the final manuscript. L.D. and K.P. contributed equally as last author.

Acknowledgements

We would like to thank Roos Colman (Cell Biostatistics, Ghent University) for offering statistical support and advice.

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Funding

The European Palliative Care Cancer Symptom (EPCCS) study is a collaborative effort between the European Palliative Care Research Centre (PRC) and the European Association for Palliative Care – Research Network (EAPCS-RN). The study was partially funded by grant no. 6070 from the joint Research Council at Norwegian University of Science and Technology (NTNU) and St. Olavs Hospital – Trondheim University Hospital. The first author has received funding from the European Union's Seventh Framework Programme FP7/2007-2013 (grant no. 602541). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Part II

End-of-life communication and information provision in people with advanced cancer

4

End-of-life communication in advanced cancer: international trends between 2009 and 2014

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This chapter is also published as an article in: *BMJ Supportive & Palliative Care* 2020; 1-12. Online ahead of print. [2020 SCI impact factor 3.568; journal ranking Q2; ranking n° 35 of 107 in HEALTH CARE SCIENCES & SERVICES]

ABSTRACT

Objective: To examine trends in end-of-life communication with cancer patients in general practice.

Methods: Mortality follow-back survey among GPs in representative epidemiological surveillance networks in Belgium (BE), the Netherlands (NL) and Spain (ES) in 2009-2010 (ES: 2010-2011) and 2013-2014. Using a standardized form, GPs registered all deceased adult patients in their practice and reported for five end-of-life care topics whether they had been discussed with the patient. Non-sudden cancer deaths were included (n=2306; BE: 1233; NL: 729; ES: 344).

Results: A statistically significant increase was found between 2009/2010 and 2014 in the prevalence of communication about diagnosis (from 84% to 94%) and options for end-of-life care (from 73% to 90%) in BE, and in GPs' awareness of patients' preferences for medical treatment and a proxy decision-maker in BE (from 41% and 20% up to 53% and 28%) and the NL (from 62% and 32% up to 70% and 52%). Communication about options for end-of-life care and psychosocial problems decreased in the NL (from 88% and 91% down to 73%) and ES (from 76% and 77% down to 26% and 39%).

Conclusion: Considerable change in GP-patient communication seems possible in a relatively short time-span, but communication cannot be assumed to increase over time. Increasing specialization of care and task differentiation may lead to new roles in communication for healthcare providers in primary and secondary care. Improved information sharing between GPs and other healthcare providers may be necessary to ensure that patients have the chance to discuss important end-of-life topics.

4.1 INTRODUCTION

Despite the progress made over the past decade in prevention and treatment, cancer remains the second leading cause of death in the European Union, accounting for more than one quarter of all deaths.[1] With an aging population that continues to grow, it is anticipated that the cancer incidence and mortality will rise further in the coming years. As a result, more people with cancer will require palliative care.[2]

High-quality palliative care requires that physicians engage in meaningful patient-centred communication,[3,4] which has several aims including fostering an interpersonal relationship, exchanging appropriate information and responding to uncertainty and emotions.[5] Effective physician-patient communication has been related to favourable patient outcomes, such as better understanding of the illness, care and treatment options,[6] adherence to treatment,[5,7] and satisfaction with end-of-life care.[5,8] Inadequate communication is associated with adverse outcomes including emotional distress and worsening of symptoms.[9]

Communication between healthcare providers and patients in oncology has often been shown to be infrequent and suboptimal.[10,11] Possible barriers for physicians to engage in effective end-of-life communication include a natural reluctance to raise this subject, lacking knowledge or training in this area, and inadequate structural support for advance care planning (ACP).[12,13] In Europe, patient-centred communication and ACP have received increasing policy attention over the last years, with efforts made in many countries to implement training, programmes and guidelines for palliative care.

In light of these developments, this study aims to examine trends in end-of-life communication between GPs and people with advanced cancer in three European countries – Belgium, the Netherlands, and Spain – from 2009 to 2014, based on data collected by general practitioner (GP) networks. Belgium, the Netherlands and Spain are all considered to be at the highest level of palliative care development, i.e., advanced integration into mainstream service provision.[14] Since 2000, efforts have been made in Belgium and the Netherlands to increase opportunities for palliative care training, as well as implementing programs and constructing guidelines to improve end-of-life communication practices.[14-16] In Spain, palliative care has continued to develop and has been integrated in educational programmes,[14] but without such a specific focus on ACP or communication. However, it is likely that different cultural traditions, attitudes towards the end of life,[17] health care systems, policies and available resources[14,18] affect end-of-life communication practices. Cross-country comparative studies focusing on aspects of end-of-life communication among individuals with cancer are scarce, although previous research has indicated that European countries vary substantially with regard to the process and content of physicians' discussions with terminally ill patients.[19]

Because GPs play a crucial role in the coordination and delivery of palliative care, they are well-placed to initiate end-of-life conversations with their patients. General practice is relatively easily accessible in the studied countries. In the Netherlands and Spain, GPs serve as gatekeepers for health care delivery – they act as referral and care coordinators.[20,21] Patients are registered with a specific GP and do not have direct access to secondary or specialist care. In Belgium, GPs have a central coordinating role in patient care but do not have a gatekeeper function, but GPs are the ones who contact palliative home care teams when necessary.[21]

Our study explores whether conversations about topics related to end-of-life care with people with cancer in primary care have become more frequent between 2009 and 2014. The specific research questions are:

1. Did the percentages of people with cancer with whom end-of-life topics (diagnosis, options for end-of-life care, psychological or social problems, preference for medical treatment in the final phase of life, preference for a proxy decision-maker) were discussed change between 2009 and 2014 in Belgium, the Netherlands and Spain, and in what direction?
2. Were there differences in the time trends in GP-patient end-of-life communication with respect to age, gender, longest place of residence, and place of death?

4.2 METHODS

Study design

This study uses data from Belgium, the Netherlands, and Spain (Castile and León) collected as part of the European Sentinel Network Monitoring End-of-Life Care (EURO SENTIMELC) study, an ongoing mortality follow-back study designed to retrospectively monitor end-of-life care in population-based samples of deaths in different countries.[21] Data were collected through existing representative GP Sentinel Networks, epidemiological surveillance networks consisting of GP practices or community-based physicians who voluntarily and continuously monitor health problems occurring in the population. In each country, GPs were selected to form a representative national sample of the total GP population and invited to participate in the networks by national public health and/or research institutes. By comparing the characteristics of GPs in the Sentinel Networks to the general population of GPs – such as age, gender and geographical distribution – the responsible institutes ensure continued representativity of the networks. Patient data was anonymized by the GPs; GP data was anonymized by the responsible institute during data cleaning. Participating GPs provided weekly reports on every adult patient in their practice who had died during the past week as part of a larger public health questionnaire. In the Netherlands, elderly care physicians who are responsible for the care of long-term care facility residents are not part of the GP Sentinel Network; this exact physician role does not exist in Belgium and Spain. Data used in this study were collected in 2009, 2010, 2013 and 2014 in Belgium and the Netherlands, and in 2010, 2011, 2013 and 2014 in Spain. More details on the data collection and study design are described elsewhere.[21]

Study population

We included all people registered by the participating GP practices who died of cancer (according to ICD-10 code), for a total of n=2627. People whose death was classified by the GPs as 'sudden and totally unexpected' and those for whom this information was missing were excluded, leaving a sample that was eligible for palliative care (n=2306).

Questionnaire

Using a standardized registration form consisting of structured and closed-ended items, GPs collected demographic characteristics (age at death, gender, longest place of residence in the last year of life, place of death), cancer type (coded according to ICD-10), and whether or not death was sudden and unexpected. Additionally, the following questions were asked regarding end-of-life communication:

1. Were the following topics addressed during your conversations with the patient?
   Diagnosis – the answer options were 'yes' or 'no'.
   Options for end-of-life care – the answer options were 'yes' or 'no'. In 2009-2010, this item was phrased as 'options for palliative care', in 2013-2014 as 'options in terms of end-of-life care', to be more in line with quality indicator measurement tools developed for general palliative care.[22]
   Psychological or social problems – the answer options were 'yes' or 'no'. In 2009-2010, these concepts were measured by two separate items which were combined for this analysis.
2. Did the patient ever express wishes about a medical treatment that he/she would or would not want in the final phase of life? The answer options were 'yes', 'no' or 'don't know'.
3. Did the patient ever express a wish about who was to make decisions regarding medical treatments or activities in his/her place, in the event he/she would no longer be able to speak for him/herself? The answer options (more than one possible) were 'yes, in writing', 'yes, verbally', 'no' or 'don't know'.

Statistical analyses

If the GP indicated 'don't know' as an answer to question 2 or 3, this was coded as 'no'.

Pearson's chi-square tests, Fisher's exact tests, or analysis of variance (ANOVA) were performed to test for differences in patient characteristics (age at death, gender, cancer type, longest place of residence in the last year of life, place of death) between years. Bivariate Mantel-Haenszel tests were calculated to detect linear trends in the proportion of people with cancer with whom any of the five studied end-of-life care topics were discussed between 2009 and 2014. Multivariable trend analyses controlling for age, gender, cancer type, longest place of residence in the last year of life, and place of death were used to test for linear trends in proportions through the SPSS UNIANOVA procedure, specifying a polynomial contrast for the variable *year*. A significant result on this test provides strong evidence for a linear relationship between year and topic discussed, as the number of patients with whom a topic was discussed in later years was significantly above what might be expected if there was no relationship between the variables. A power analysis was conducted for each variable in each country, assuming a medium effect-size, showing that power was above 95% for all variables in Belgium, preferences for medical treatment and a proxy decision-maker in the Netherlands and diagnosis in Spain. Power was between 68% and 78% for the remaining variables in the Netherlands, and below 55% for the remaining variables in Spain, suggesting the trend analysis for these variables may be underpowered. Statistical significance was set at $p<.05$. All analyses were performed using IBM SPSS Statistics version 24.0.

Ethics

For Belgium, ethics approval was obtained from the Ethical Review Board of Brussels University Hospital of the Vrije Universiteit Brussel (VUB). Formal approval for this research project by a medical ethics committee was not required in The Netherlands according to the Medical Research (Human Subjects) Act (WMO), but permission for the study was sought and obtained from the board of the NIVEL network. The NIVEL Primary Care Database extracts data according to strict guidelines for the privacy protection of patients and GPs. Ethics approval was not required for posthumous collection of anonymous patient data in Spain, according to the legislation of this country.

4.3 RESULTS

Characteristics of the study population

A total of 2306 cancer decedents were included (BE=1233; NL=729; ES=344; *Table 1*). The median age at death was between 73 and 78 years. In general, the most common cause of death was lung cancer (BE: 21-25%; NL: 22-29%; ES: 17-20%). The majority of people lived at home in the last year of life (BE: 81-88%; NL: 88-91%; ES: 92-97%) and in general home was the most common place of death (BE: 31-38%; NL: 54-62%; ES: 41-50%). In Spain, the percentage of women was considerably lower than the percentage of men (30-34% across years). Additional data analysis showed that this relatively large gender imbalance was present only for those who died of cancer, regardless of whether death was 'sudden and totally unexpected', possibly because in Spain, 60% of new cancers are diagnosed in men.[23]

Trends in the proportion of people with whom end-of-life care topics were discussed

Belgium was the only country to see a significant increase in the percentage of people with whom their diagnosis was discussed between 2009 and 2014 (from 84% to 94%, p<.01) (*Table 2*; *Figure 1*). In multivariable regression models controlling for age, gender, cancer type, longest place of residence in the last year of life, and place of death, this increase was significant for all age groups, both genders, those who lived at home and in a long-term facility in the last year of life, and those who died at home, in a hospital, and in a long-term care facility (*Table 3*).

The percentage of people with whom options for end-of-life care were discussed showed an increasing trend in Belgium between 2009 and 2014 (from 73% to 90%, p<.001), but decreased significantly in the Netherlands between 2009 and 2014 (from 88% to 73%, p<.001) and in Spain between 2010 and 2014 (from 76% to 26%, p<.001) (*Table 2*; *Figure 1*). In multivariable regression, the increase in Belgium was significant for all age groups and both genders, for those who lived at home in the last year of life, and for those who died at home, in a hospital, and in a palliative care unit or hospice (*Table 3*). In the Netherlands, the decreasing trend was significant for those aged 65-84 and 85+, both genders, those who lived at home in the last year of life, and those who died at home and in a palliative care unit or hospice. In Spain, the decrease was significant for both genders, those aged 65-84, those who lived at home in the last year of life, and those who died at home.

The percentage of people with whom psychological or social problems were discussed decreased significantly over time in both the Netherlands (from 91% to 73%, p<.001) and Spain (from 77% to 39%, p<.001). In multivariable regression, this decrease was significant in the Netherlands for all age groups, both genders, those who lived at home and those who lived in a long-term care facility during the last year of life and for all place of death groups (*Table 3*). In Spain, the decrease was significant for those aged 18-64, females, those who lived at home in the last year of life, and those who died at home. While overall, no decreasing trend in communication about psychological or social problems was found in Belgium between 2009 and 2013 (*Table 2*), multivariable regression showed that there was a significant decrease for those aged 18-64, and those who died at home.

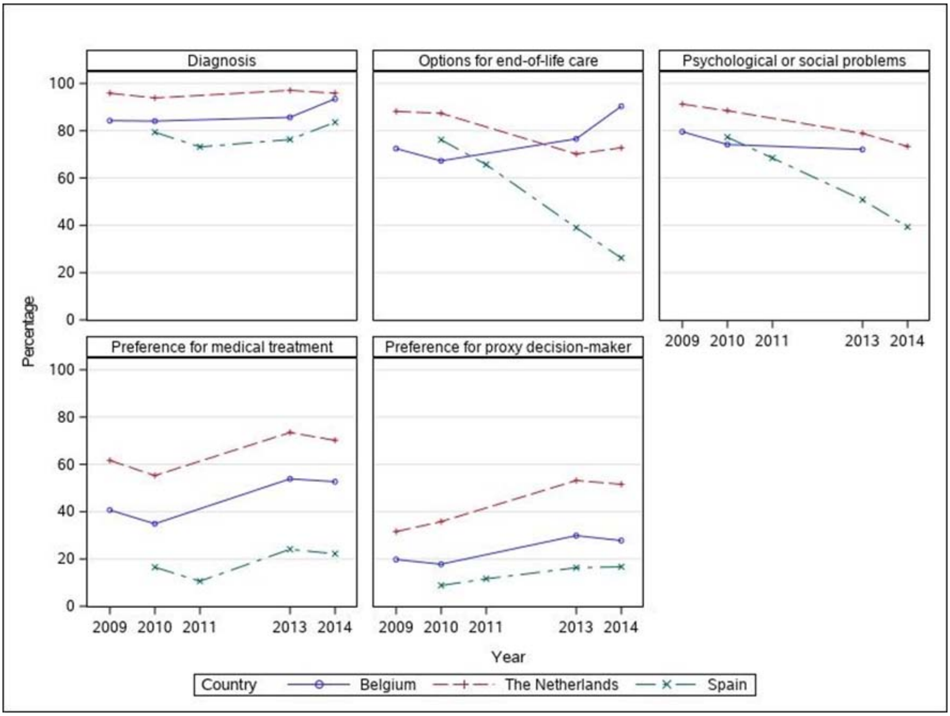

Figure 1. Trends in communication between general practitioners (GPs) and people with advanced cancer about end-of-life care topics in Belgium, the Netherlands and Spain, 2009-2014. Showing percentages of patients with whom certain end-of-life care topics were discussed, according to the GP, per year. Blue line shows Belgium, red line shows the Netherlands, green line shows Spain.

Trends in preferences known for medical treatments at the end of life

The percentage of people for whom the GP was aware of a preference for medical treatment they would or would not want at the end of life increased in Belgium (from 41% to 53%, p<.001) and in the Netherlands between 2009 and 2014 (62% to 70%, p<.01). No significant trend was found for Spain (*Table 2*; *Figure 1*). In multivariable regression, the increase in Belgium was significant for those aged 18-64 and those aged 65-84, both genders, those who lived at home in the last year of life, and those who died at home and in a palliative care unit or hospice (*Table 4*). In the Netherlands, the increase was significant for those aged 18-64 and 65-84, males, those who lived at home in the last year of life, and those who died at home, in a hospital, and in a palliative care unit or hospice.

Table 1. Characteristics of the study population: people with cancer who died non-suddenly in Belgium, the Netherlands and Spain, 2009-2014 (*n*=2306)

	Belgium				
	2009	**2010**	**2013**	**2014**	
	N=303	*N*=292	*N*=336	*N*=302	
	n (%)	*n* (%)	*n* (%)	*n* (%)	*P* [*]
Age at death (years), median (95% CI)	74 (72-76)	75 (73-77)	77 (75-79)	77 (74-79)	**.02**
Gender, female	129 (43)	138 (47)	160 (48)	138 (46)	.58
Primary cancer site					
Lung	76 (25)	72 (25)	72 (21)	70 (23)	.69
Colorectal	33 (11)	36 (12)	47 (14)	42 (14)	.61
Breast	22 (7)	29 (10)	37 (11)	19 (6)	.12
Prostate	10 (3)	15 (5)	26 (8)	20 (7)	.09
Other	162 (54)	140 (48)	154 (46)	151 (50)	.26
Longest place of residence in last year[±]					
Home	261 (87)	255 (88)	288 (86)	243 (81)	.10
Long-term care facility	34 (11)	31 (11)	38 (11)	51 (17)	.07
Place of death[±]					
Home	94 (31)	102 (35)	126 (38)	95 (32)	.28
Hospital	103 (34)	98 (34)	95 (28)	90 (30)	.30
PCU/hospice	65 (22)	57 (20)	62 (19)	45 (15)	.20
Long-term care facility	38 (13)	33 (11)	51 (15)	68 (23)	**<.01**

Missing data <1.5% for all variables.

[*] Bivariate Pearson's chi-squared tests or Fisher's exact tests, except for age (ANOVA).

[±] Categories 'living elsewhere' (Belgium: *n*=25; the Netherlands: *n*=9; Spain: *n*=6) and 'died elsewhere' (Belgium: *n*=3; the Netherlands: *n*=4) not shown in table. 'Home' indicates living in own home or with family.

Trends in preferences known for a proxy decision-maker

The percentage of people for whom the GP was aware of a preference for a proxy decision-maker at the end of life increased in Belgium (from 20% to 28%, p<.001) and in the Netherlands between 2009 and 2014 (from 32% to 52%, p<.001). Spain did not show a significant trend (*Table 2*; *Figure 1*). In multivariable regression, the increase in the percentage of people for whom the GP was aware of a preference for a proxy decision-maker at the end of life in Belgium was significant in those aged 18-64, those who lived in a long-term care facility in the last year of life, and those who died at home (*Table 4*). In the Netherlands, the increase was significant in those aged 65-84 and 85+, males, those who lived at home in the last year of life, and those who died at home.

	The Netherlands					Spain				
	2009	2010	2013	2014		2010	2011	2013	2014	
	N=157	*N*=189	*N*=190	*N*=193		*N*=80	*N*=86	*N*=88	*N*=90	
	n (%)	*n* (%)	*n* (%)	*n* (%)	*P**	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*P**
	73 (70-75)	73 (72-76)	73 (71-75)	75 (72-76)	.23	77.5 (73-81)	77 (74-81)	78 (77-83)	76.5 (72-79)	.18
	83 (53)	76 (41)	89 (47)	93 (48)	.15	24 (30)	28 (33)	30 (34)	31 (34)	.93
	34 (22)	46 (27)	40 (24)	52 (29)	.41	15 (20)	15 (19)	14 (17)	16 (18)	.96
	12 (8)	28 (16)	23 (14)	21 (12)	.12	21 (28)	12 (15)	7 (8)	3 (3)	**<.001**
	26 (17)	8 (5)	18 (11)	11 (6)	**<.01**	5 (7)	5 (6)	13 (15)	15 (17)	**.05**
	11 (7)	13 (8)	14 (8)	6 (3)	.25	8 (11)	9 (11)	5 (6)	3 (3)	.18
	74 (47)	78 (45)	75 (44)	89 (50)	.73	27 (36)	40 (49)	46 (54)	50 (58)	**.03**
	143 (91)	166 (90)	167 (88)	173 (91)	.84	73 (92)	79 (94)	78 (92)	86 (97)	.55
	14 (9)	18 (10)	19 (10)	13 (7)	.68	6 (8)	2 (2)	5 (6)	2 (2)	.26
	84 (54)	110 (58)	114 (60)	118 (62)	.45	39 (49)	42 (50)	30 (41)	37 (41)	.49
	28 (18)	30 (16)	31 (16)	33 (17)	.96	23 (29)	27 (32)	23 (31)	24 (27)	.86
	27 (17)	27 (14)	23 (12)	23 (12)	.47	10 (13)	13 (16)	17 (23)	24 (27)	.08
	17 (11)	22 (12)	21 (11)	15 (8)	.62	8 (10)	2 (2)	4 (5)	5 (6)	.23

'Long-term care facility' includes residential care home in Belgium, residential home for older people in the Netherlands and Spain, (infrequently) nursing home in the Netherlands. 'Hospital' excludes PCU and nursing home unit in hospital.

ANOVA: analysis of variance. PCU: palliative care unit.

Table 2. Trends in communication between general practitioners and people with advanced cancer about end-of-life care topics in Belgium, the Netherlands and Spain, 2009-2014 (*n*=2306)

	Belgium				
	2009	**2010**	**2013**	**2014**	
	N=303	*N*=292	*N*=336	*N*=302	
	n (%)	*n* (%)	*n* (%)	*n* (%)	*P**
Topics discussed					
Diagnosis	241 (84)	233 (84)	275 (86)	245 (94)	**<.01**
Options for end-of-life care	206 (73)	183 (67)	200 (77)	161 (90)	**<.001**
Psychological or social problems	227 (80)	204 (74)	168 (72)	---	.07
Preference for medical treatment	123 (41)	102 (35)	178 (54)	158 (53)	**<.001**
Preference for proxy decision-maker	60 (20)	52 (18)	99 (30)	84 (28)	**<.001**

Missing data: BE 5%, NL 6%, ES 20% for ‘diagnosis’; BE 17%, NL 6%, ES 21% for ‘options for end-of-life care’; BE 15%, NL 9%, ES 25% for ‘psychological or social problems’; BE 1%, NL 1%, ES 1% for ‘preference for medical treatment’; BE 0%, NL 1%, ES 1% for ‘preference for proxy decision-maker’.

The Netherlands					Spain				
2009	**2010**	**2013**	**2014**		**2010**	**2011**	**2013**	**2014**	
N=157	*N*=189	*N*=190	*N*=193		*N*=80	*N*=86	*N*=88	*N*=90	
n (%)	*n* (%)	*n* (%)	*n* (%)	*P**	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*P**
142 (96)	169 (94)	166 (97)	162 (96)	.45	54 (79)	52 (73)	45 (76)	51 (84)	.49
127 (88)	152 (87)	120 (70)	123 (73)	**<.001**	48 (76)	46 (66)	23 (39)	16 (26)	**<.001**
136 (91)	154 (89)	135 (79)	124 (73)	**<.001**	51 (77)	50 (69)	30 (51)	24 (39)	**<.001**
95 (62)	104 (55)	139 (74)	134 (70)	**<.01**	13 (17)	9 (11)	21 (24)	20 (22)	.06
49 (32)	67 (36)	100 (53)	98 (52)	**<.001**	7 (9)	10 (12)	14 (16)	15 (17)	.08

* Bivariate Mantel-Haenszel tests for linear trends.

BE: Belgium. NL: the Netherlands. ES: Spain.

Table 3. Trends in communication between general practitioners and people with advanced cancer about the diagnosis, options for end-of-life care and psychological or social problems by patient group in Belgium, the Netherlands and Spain, 2009-2014 (*n*=2306)

	Diagnosis			
	2009*	2014		
	BE: *N*=1201 NL: *N*=710 ES: *N*=323		%-point change	
Patient group	%	%		$p^{\pm}$
Age (years)				
18-64				
Belgium	89	95	+6 pp	**<.001**
The Netherlands	100	97	-3 pp	.68
Spain	75	94	+19 pp	.92
65-84				
Belgium	89	95	+7 pp	**<.001**
The Netherlands	97	95	-1 pp	.16
Spain	80	86	+7 pp	.61
85+				
Belgium	64	89	+25 pp	**<.001**
The Netherlands	85	97	+12 pp	.55
Spain	84	43	-42 pp	---
Gender				
Male				
Belgium	84	93	+8 pp	**<.001**
The Netherlands	96	93	-3 pp	.07
Spain	82	87	+5 pp	.47
Female				
Belgium	84	95	+11 pp	**<.001**
The Netherlands	96	99	+3 pp	.75
Spain	74	78	+3 pp	.69
Longest place of residence‡				
Home				
Belgium	86	95	+8 pp	**<.001**
The Netherlands	96	96	+1 pp	.39
Spain	81	85	+4 pp	.60
Long-term care facility				
Belgium	63	88	+25 pp	**<.001**
The Netherlands	100	91	-9 pp	.45
Spain	60	50	-10 pp	---

Options for end-of-life care				Psychological or social problems			
2009*	2014			2009*	2014		
BE: *N*=1194 NL: *N*=702 ES: *N*=320		%-point change		BE: *N*=931 NL: *N*=729 ES: *N*=344		%-point change	
%	%		$p^{\pm}$	%	%		$p^{\pm}$
78	92	+14 pp	**<.001**	87	---	-21 pp	**<.001**
85	74	-11 pp	.16	93	81	-12 pp	**<.001**
94	28	-66 pp	.07	81	44	-37 pp	**<.01**
78	92	+14 pp	**<.001**	78	---	-2 pp	.89
90	69	-21 pp	**<.001**	91	71	-20 pp	**<.001**
77	31	-47 pp	**<.01**	78	39	-39 pp	.12
46	85	+39 pp	**<.001**	68	---	-5 pp	.07
85	83	-2 pp	**.05**	90	73	-17 pp	**<.01**
50	---	---	---	71	29	-43 pp	---
73	89	+16 pp	**<.001**	78	---	-9 pp	.10
96	93	-15 pp	**<.01**	87	75	-12 pp	**<.001**
76	26	-49 pp	**.01**	77	42	-35 pp	.74
71	93	+21 pp	**<.001**	82	---	-6 pp	.18
91	75	-16 pp	**<.001**	95	71	-24 pp	**<.001**
78	26	-52 pp	**<.01**	79	35	-44 pp	**<.001**
75	92	+17 pp	**<.001**	81	---	-4 pp	.25
87	72	-15 pp	**<.001**	91	76	-15 pp	**<.001**
81	27	-54 pp	**<.001**	77	41	-36 pp	**.04**
47	80	+33 pp	.08	67	---	-27 pp	.26
100	82	-18 pp	---	92	36	-56 pp	**.01**
20	---	---	---	80	---	---	---

Table 3. Continued

	Diagnosis			
	2009*	2014		
	BE: *N*=1201 NL: *N*=710 ES: *N*=323		%-point change	
Patient group	%	%		*p*±
Place of death‡				
Home				
Belgium	89	95	+6 pp	**<.001**
The Netherlands	98	96	-1 pp	.08
Spain	94	82	-12 pp	.32
Hospital				
Belgium	87	96	+10 pp	**<.001**
The Netherlands	92	100	+8 pp	.15
Spain	65	89	+24 pp	.74
PCU/hospice				
Belgium	84	91	+6 pp	.19
The Netherlands	96	96	-17 pp	.39
Spain	67	88	+22 pp	.41
Long-term care facility				
Belgium	68	89	+22 pp	**<.001**
The Netherlands	94	85	-9 pp	**.02**
Spain	67	50	-17 pp	---

Missing data for independent variables <3%. Missing data for dependent variables: BE 5%, NL 6%, ES 20% for 'diagnosis'; BE 17%, NL 6%, ES 21% for 'options for end-of-life care'; BE 15%, NL 9%, ES 25% for 'psychological or social problems'.

* The year 2010 is shown for Spain since data were not available for 2009.

± Multivariable trend analysis controlled for age, gender, primary cancer site, longest place of residence in the last year of life, place of death. In some cases significance tests could not be performed due to small *n*.

Options for end-of-life care				Psychological or social problems			
2009*	2014			2009*	2014		
BE: *N*=1194 NL: *N*=702 ES: *N*=320		%-point change		BE: *N*=931 NL: *N*=729 ES: *N*=344		%-point change	
%	%		*p*‡	%	%		*p*‡
88	94	+6 pp	**<.01**	88	---	-10 pp	**<.01**
91	78	-14 pp	**<.001**	90	80	-11 pp	**<.001**
88	41	-47 pp	**<.01**	82	50	-32 pp	**.02**
62	92	+30 pp	**<.01**	79	---	-8 pp	.40
77	39	-38 pp	.85	100	78	-22 pp	**<.01**
81	28	-54 pp	.13	61	28	-33 pp	.12
79	86	+6 pp	**<.01**	73	---	+6 pp	.43
88	82	-6 pp	**.02**	85	64	-21 pp	**.05**
63	12	-51 pp	.97	100	47	-53 pp	.27
47	83	+36 pp	.79	74	---	-30 pp	.33
88	77	-11 pp	.77	94	39	-55 pp	**<.001**
29	---	---	---	72	---	---	---

‡ 'Home' indicates living in own home or with family. 'Long-term care facility' includes residential care home in Belgium, residential home for older people in the Netherlands and Spain, (infrequently) nursing home in the Netherlands. 'Hospital' excludes PCU and nursing home unit in hospital.

BE: Belgium. NL: the Netherlands. ES: Spain. %-point and pp: percentage point (calculated using the first and last available year).

Table 4. Trends in awareness by general practitioners (GPs) of preferences of people with advanced cancer for medical treatment and for a proxy decision-maker by patient group in Belgium, the Netherlands and Spain, 2009-2014 (*n*=2306)

	Patient expressed preference for medical treatment			
	2009[*]	**2014**		
	BE: *N*=1233 NL: *N*=729 ES: *N*=344		%-point change	
Patient group	%	%		$p^{\pm}$
Age (years)				
18-64				
Belgium	42	48	+7 pp	**<.001**
The Netherlands	58	68	+10 pp	**.05**
Spain	29	36	+7 pp	.20
65-84				
Belgium	41	58	+18 pp	**<.001**
The Netherlands	63	67	+4 pp	**<.01**
Spain	17	20	+3 pp	.15
85+				
Belgium	40	46	+5 pp	.10
The Netherlands	63	83	+20 pp	.06
Spain	---	12	---	---
Gender				
Male				
Belgium	39	54	+15 pp	**<.001**
The Netherlands	51	73	+22 pp	**<.001**
Spain	20	17	-3 pp	.14
Female				
Belgium	43	52	+9 pp	**<.01**
The Netherlands	72	67	-4 pp	.11
Spain	9	32	+26 pp	.83
Longest place of residence[‡]				
Home				
Belgium	41	57	+16 pp	**<.001**
The Netherlands	64	71	+7 pp	**<.001**
Spain	18	23	+6 pp	.17

Patient expressed preference for proxy decision-maker			
2009*	2014		
	BE: N=1233 NL: N=729 ES: N=344	%-point change	
%	%		$p^{\ddagger}$
19	37	+18 pp	**.01**
36	39	+3 pp	.38
12	18	+6 pp	---
19	25	+7 pp	.62
29	51	+23 pp	**.02**
11	16	+5 pp	.51
23	26	+3 pp	.27
32	63	+31 pp	**.05**
---	18	---	---
21	35	+14 pp	.18
14	48	+35 pp	**<.001**
9	10	+1 pp	.40
18	20	+2 pp	.60
48	55	_+7 pp	.86
8	29	+21 pp	.89
19	29	+10 pp	.08
33	52	+19 pp	**<.01**
10	17	+8 pp	.51

Table 4. Continued

	Patient expressed preference for medical treatment			
	2009*	**2014**		
		BE: *N*=1233 NL: *N*=729 ES: *N*=344	%-point change	
Patient group	%	%		$p^{\pm}$
Long-term care facility				
Belgium	32	35	+3 pp	.70
The Netherlands	43	69	+26 pp	.95
Spain	---	---	---	---
Place of death‡				
Home				
Belgium	55	73	+18 pp	**<.001**
The Netherlands	76	82	+6 pp	**<.001**
Spain	21	27	+7 pp	**.02**
Hospital				
Belgium	33	33	0 pp	.71
The Netherlands	50	39	-11 pp	.05
Spain	13	25	+12 pp	.60
PCU/hospice				
Belgium	39	60	+21 pp	**<.01**
The Netherlands	35	68	+34 pp	**<.01**
Spain	20	17	-3 pp	.18
Long-term care facility				
Belgium	29	44	+15 pp	.53
The Netherlands	53	60	+7 pp	.97
Spain	---	---	---	---

Missing data for independent variables <3%. Missing data for dependent variables: BE 1%, NL 1%, ES 1% for 'preference for medical treatment'; BE 0%, NL 1%, ES 1% for 'preference for proxy decision-maker'.

* The year 2010 is shown for Spain since data were not available for 2009.

± Multivariable trend analysis controlled for age, gender, primary cancer site, longest place of residence in the last year of life, place of death. In some cases significance tests could not be performed due to small *n*.

Patient expressed preference for proxy decision-maker			
2009*	**2014**		
BE: *N*=1233 NL: *N*=729 ES: *N*=344		%-point change	
%	%		*p*‡
27	22	-5 pp	**.04**
14	39	+24 pp	.80
---	---	---	---
20	41	+21 pp	**<.01**
41	66	+25 pp	**<.01**
8	16	+9 pp	.08
15	14	0 pp	.20
21	15	-6 pp	.26
4	21	+17 pp	.48
26	22	-4 pp	.13
23	46	+22 pp	.37
30	17	-13 pp	.74
24	27	+3 pp	.18
18	33	+16 pp	.14
---	---	---	---

‡ 'Home' indicates living in own home or with family. 'Long-term care facility' includes residential care home in Belgium, residential home for older people in the Netherlands and Spain, (infrequently) nursing home in the Netherlands. 'Hospital' excludes PCU and nursing home unit in hospital.
BE: Belgium. NL: the Netherlands. ES: Spain. PCU: palliative care unit. %-point and pp: percentage point (calculated using the first and last available year).

4.4 DISCUSSION AND CONCLUSION

Discussion

Our findings show that there has been a significant increase between 2009 and 2014 in the percentages of people with cancer with whom certain end-of-life care topics were discussed (diagnosis, GPs' awareness of a preference for medical treatment at the end of life, GPs' awareness of a preference for a proxy decision-maker). This is in line with the overall enhanced attention to patient-centred communication and ACP initiatives, focusing on the process of discussing personal goals and wishes for care and treatment at the end of life.[14-16] However, we also found some significant decreases for other topics (options for end-of-life care, psychological or social problems). In general, these trends were found across countries and across patient groups. Although some differences between groups persist, this study shows that changes in the likelihood of communication between GPs and people with cancer are widespread and indicative of a change in the general population. This may also mean that similar findings could be expected for other disease groups.

To our knowledge, this study is the first trend analysis on end-of-life communication practices in primary care in Europe for people with advanced cancer. In line with previous research[19,24] and our expectations, the international comparison of Belgium, the Netherlands and Spain allowed us to see that while overall trends were similar in many ways, there are considerable cross-country differences in the prevalence and magnitude of change in communication related to end-of-life care, including the overall higher frequency of end-of-life conversations in the Netherlands and Belgium compared with Spain. Cultural variation may play a role in these overall differences, with Southern European cultures having a stronger tendency to avoid discussions that cause distress or discomfort, trying not to take away hope.[25,26]

Diagnosis was the most commonly discussed end-of-life care topic in all three countries, a finding that is consistent with results from other cross-country attitudinal research.[19] The high frequency of discussions of the diagnosis in all countries (between 84% and 96% in 2014) seems to reflect a commitment of GPs to providing people with advanced cancer with the information needed to understand their medical condition.[27] Awareness of their diagnosis creates an opening for patients to engage in a conversation about other implications of their illness, allowing patients to exercise their autonomy. Only in Belgium, the increasing trend in the proportion of patients with whom the diagnosis was discussed was statistically significant; however, in the Netherlands a ceiling effect may have been at play, with communication already being at 96% in 2009. The increase in Belgium may have been due to several initiatives taking place during the 2009-2014 period, including the implementation of enhanced reimbursement to enable GPs to spend more time with patients on consultations in which the announcement of the diagnosis takes place, additional training for doctors on communication with patients, and the publishing of a protocol for disclosing the bad news about the diagnosis drafted by a group of experts.[15,16]

We found that GPs awareness of preferences for medical treatment at the end of life and awareness of preferences for a proxy decision-maker clearly increased in Belgium (from 41% to 53%) and in the Netherlands (from 62% to 70%) between 2009 and 2014. Even though similar upward patterns were visible in Spain, these did not reach statistical significance, possibly due to low statistical power. These aspects of advance care planning have numerous benefits for patients, families and professional caregivers.[28,29]

Besides increasing trends, this study also found unexpected declines over time for some variables. The percentage of people with whom options for end-of-life care were discussed dropped between 2009 and 2014 in the Netherlands (from 88% to 73%) and to an even more extreme extent in Spain (from 74% to 26%). Furthermore, again in the Netherlands and in Spain, a decline was seen in the percentage of people with whom psychological or social problems were discussed (from 91% to 73% and from 77% to 39%, respectively). These two items were the only items which have undergone minor modifications to their formulation. This could have influenced interpretation. However, the downward trends were already visible within the first wave (from 2009 to 2010 in the Netherlands and from 2010 to 2011 in Spain) and therefore the impact of changes in phrasing may have been limited. Additionally, the new formulation of the question (from 'palliative care' to 'end-of-life care'), which was explicitly intended to allow respondents to imagine a wider range of care provided beyond specialized palliative care, could equally have been expected to result in an increase in the response. A Belgian study found that medical oncologists perceive the term 'palliative care' as a barrier to communication about end-of-life care due to the stigma associated with the term, and in Belgium we indeed saw an increase in reported communication once this term had been removed from the questionnaire.[30] However, there are also indications that the term 'end-of-life care' carries a stigma of its own in certain cultures, and is not well-defined in all contexts.[31] As such, these conflicting pressures may be responsible for some of the changes over time.

Other explanations for these unexpected decreases exist. One possible interpretation is related to an increase in the specialization of cancer care and palliative care. Due to suboptimal information transmission between GPs and specialists, it is not uncommon for GPs and their patients to lose touch during ongoing treatment and in the post-treatment phases.[32] In Spain for example, palliative care in hospitals has improved considerably over the course of this study, possibly leading to an increase in end-of-life conversations taking place in the hospital instead of the primary care setting.[14] In the Netherlands, a recent study showed that GPs were more hesitant to engage in ACP with patients who were still being treated by specialists in hospital, as these patients are often less open to discussion.[33] Numerous initiatives have been developed to make earlier integration of specialized palliative care services a reality.[34-37] Consequently, certain topics may be more frequently discussed with palliative caregivers or nurses of the palliative homecare team rather than with GPs. An interesting example is the evolving role of the oncology nurse in clinical oncology departments.[38,39] These nurses pay particular attention to the emotional impact of living with and beyond the diagnosis and its treatment through the cancer care pathway.[40] However, this does not explain why these decreases were only found for the Netherlands and Spain, and not for Belgium, where the role of the oncology nurse is well-defined and highly appreciated.[41] The way palliative care provision is organised may contribute to part of the differences. Belgium and the Netherlands are small countries where palliative care is often highly accessible, whereas in Spain, despite improvements in recent years, palliative care provision in rural areas is still lacking.[14]

The mortality follow-back study design is a robust study design to measure end-of-life care on a population level.[42] In this study recall bias was limited since GPs were instructed to complete the questionnaire within a week of the patient's death. A limitation is that although representative within this area, the Spanish Sentinel Network only covered a specific region resulting in a smaller sample and lower statistical power. Furthermore, this study only reports if topics were discussed according to the GP, and does not represent the totality of end-of-life communication with cancer patients. Perceptions of what constitutes the 'discussion' of a certain topic may differ between patients and physicians.[43] The present study examines the prevalence of discussions and can neither provide in-depth insights into patients' expectations or desires for such conversations – e.g., whether patients took the initiative for such communication themselves or whether they rely on their GP to initiate – nor into the quality of the communication process – e.g., whether communication about care preferences was started early enough that this could make a material difference to the quality of end-of-life care. Finally, due to the low statistical power for some analyses, particularly in Spain, it is possible that the significance of some results is underestimated.

This study shows that initiatives to increase end-of-life communication can be ambitious and aim at significant change in clinical practice in a short time. However, the prerequisites for successful interventions are still unknown, while challenges to continued high levels of communication between GPs and patients are also apparent. For instance, the ongoing increase in the specialization of cancer care and palliative care and subsequent task differentiation between healthcare professionals pave the way for new roles and responsibilities in primary and secondary care. This will require better communication between healthcare providers in order to maintain good communication with patients. Future research should provide a broader picture including ACP as a whole as well as including the various healthcare providers.

Conclusion

Broad changes, both increasing and decreasing, were found between 2009 and 2014 in the number of people with cancer with whom certain end-of-life care topics were discussed according to GPs in Belgium, the Netherlands and Spain. Despite international differences that appear to persist over time, end-of-life communication in primary care in Europe can change substantially in a relatively short period of time across patient groups.

ADDITIONAL INFORMATION

Acknowledgements

The authors wish to acknowledge all participating GP practices for providing the data for this study throughout the years, for which they received no financial incentives.

Competing interest

None declared.

Funding

Data collection was funded by the Belgian Scientific Institute of Public Health (now Sciensano), the Netherlands Institute for Health Services Research and the Regional Ministry of Health of Castile and León (Spain). The first author received funding from the European Union's Seventh Framework Programme FP7/2007-2013 (grant agreement no. 602541). The funding agencies were not involved in the decision to write or submit this manuscript.

Data availability statement

Data may be made available upon request to the relevant national institute.

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5

Information provision as evaluated by people with cancer and bereaved relatives: a cross-sectional survey of 34 specialist palliative care teams

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This chapter is also published as an article in: *Patient Education and Counseling* 2019; **102**(4): 768-75. [2019 SCI impact factor 2.607; journal ranking Q1; ranking n° 16 of 108 in SOCIAL SCIENCES, INTERDISCIPLINARY]

ABSTRACT

Objective: To explore how individuals with cancer and bereaved relatives evaluate information provision by specialist palliative care services (PCSs).

Methods: A cross-sectional survey was conducted within four multidisciplinary palliative homecare teams (HCTs), 17 hospital-based palliative care units (PCUs) and 13 hospital-based mobile palliative support teams (PSTs) in Belgium. During four measurement periods, structured questionnaires were administered to people being guided by PCSs and relatives of patients who had died while under the care of PCSs.

Results: In total, 628 patients (80%) and 980 relatives (55%) responded; 73-82% and 75-77% respectively reported having received the right amount of information. Compared with those receiving care within a PCU, those being supported by a PST were more likely to report suboptimal information provision and decision-making. Relatives of those who had died while under the guidance of a PST were also more likely to report suboptimal information provision than their PCU counterparts.

Conclusion: Although information provision to cancer patients and relatives being supported by PCSs is generally evaluated positively, evaluations depend on the type of service.

Practice implications: Information provided within PCUs offering highly personalized, continuous care appears to both groups more satisfactory than that provided by palliative care teams mainly supporting care staff.

5.1 INTRODUCTION

Palliative care is an approach that focuses on improving the quality of life of seriously ill individuals and those close to them in relation to the problems associated with life-threatening illness.[1] It integrates psychosocial and spiritual/existential aspects of patient care and offers a support system to help them cope with illness and bereavement. People who are confronted with life-threatening illness have to make several decisions about their care. In order to ensure they make well-informed decisions that are congruent with their preferences, it is necessary that they and those close to them have an accurate understanding of the disease, prognosis, treatment, and care options.[2-7] This requires both the provision of adequate information by professional caregivers and its successful comprehension by those receiving it.[3] Therefore, the quality of communication and information provision are key elements within the field of palliative care.

In Europe, the majority of those receiving specialist palliative care are people with cancer.[8] A previous review of information and decision-making preferences in people with advanced cancer has shown that most of them want to be fully informed and that about two-thirds want to be actively involved in decision-making about their care.[9] However, other studies have indicated that there is considerable variation in how people desire to be informed about their diagnosis, expected disease course and end-of-life decisions.[10,11] Particularly at the end of life, when their condition has worsened, people may express ambivalence about end-of-life discussions[12,13] or prefer gradual information tailored to their emotional responses[10] and a less active role in decision-making.[11,14] Hence it is extremely important to take individual needs, preferences and capabilities into account when providing disease-related information and when engaging people in decision-making .[7,15]

This study aims to evaluate the experience of information provision of people – both those with cancer and those close to them – who are under the guidance of specialist palliative care services (PCSs). PCSs are committed to and trained in supporting individuals near the end of life. It can be expected therefore that those they cater to will receive a satisfactory amount of information about their disease and end-of-life care, and that they are given the opportunity to be involved in decision-making about their care. The organization of palliative care services in Europe varies across countries, but can generally be classified based on the place of provision, through hospitals as inpatient or outpatient basis or in the form of home-based care.[16] In Belgium, multidisciplinary mobile palliative homecare teams support general practitioners – who have a central role in coordinating care at the end of life – and nurses in providing palliative care for people who wish to stay at home[17-20] and those living in care homes. Hospitals operate two different types of PCSs: 1) palliative care units, i.e., separate wards within a hospital where patients and families with more complex needs that cannot be met in the home or care home setting are offered individual and continuous palliative care,[17-21] and 2) mobile palliative support teams, i.e., teams consisting of specifically trained personnel who act as a supportive care consultancy to the different wards in the hospital.[17,18,22,23]

To our knowledge, few studies to date have examined information provision, including information about end-of-life care, by different types of PCSs from the perspective of both people with advanced cancer and those close to them. Family members can have a central role in decisions about cancer treatment, especially in cases where the individual loses decision-making capacity close to death.[24,25] In order to participate effectively in decision-making, it is essential that they are provided with sufficient and appropriate information.

Our study addresses the following research questions:

1. How do people with cancer being supported by PCSs evaluate the amount of information provided to them about their illness and end-of-life care and their involvement in decision-making about their care?
2. How do those close to people with cancer who had died while under the guidance of PCSs evaluate the amount of information provided to them about their relative's illness and treatment?
3. Are there differences between these evaluations with respect to patient characteristics (age, gender), length of guidance, and type of PCS?

5.2 METHODS

Study design and study population

This national cross-sectional survey was part of the more comprehensive Quality Indicators for Palliative Care (QPAC) Study.[26-28] Questionnaires were administered at one moment in time during four measurement periods (November 2014, May 2015, November 2015 and May 2016) within 34 specialist palliative care services (PCSs), four of 15 (20%) multidisciplinary mobile palliative homecare teams, 17 of 29 (59%) hospital-based palliative care units and 13 of 83 (17%) hospital-based mobile palliative support teams in Flanders, Belgium. The current study focuses on the survey questions related to information provision as evaluated by patients and relatives.

Only those with a diagnosis of cancer were included in the analyses. We used data from two different respondent groups: 1) people with cancer (age ≥18 years) being guided by PCSs at the time of the measurement, and 2) the people most relevant to people who had died of cancer (e.g., partner, family member or friend most closely involved). The data were collected by all participating teams. People with cancer and bereaved relatives were identified based on the questionnaire for patients (question about main diagnosis) and on checklists that were completed by the coordinators of the participating palliative care teams for all patients included in the measurement. These checklists contained information about the diagnosis (cancer/non-cancer), demographic information (age, gender), date of referral to the PCSs and the date of death for those who had already died. Checklist and questionnaire data were linked using unique anonymized identification numbers.

Measurement procedure

The measurement procedure followed a snapshot approach: a cross-sectional inclusion method was used during every measurement period which required the palliative care teams to make a random selection of two groups of patients on one given day (i.e., the day of the assessment) with a maximum of 50 in each group, people who were under the guidance of PCSs on that specific day and people who had died while under the guidance of PCSs between the previous four weeks and four months [26].

For the first group, questionnaires were sent to the person with cancer (or to a representative if they were unable to fill out the questionnaire). For the second group, questionnaires were sent to the most significant relatives, mostly the partners. Completed questionnaires were gathered by the palliative care teams and sent to the researchers for data analysis.

Questionnaires

Questionnaire items were either based on existing questionnaires or developed by the researchers in cooperation with an expert panel.[28]

The following questions on information provision were asked to patients:

1. Are you getting enough information about the diagnosis? Answer options: ‘less than necessary’, ‘just the right amount’, ‘more than necessary’.
2. Are you getting enough information about the course of the disease? Answer options: ‘less than necessary’, ‘just the right amount’, ‘more than necessary’.
3. Are you getting enough information with regard to end-of-life care? Answer options: ‘less than necessary’, ‘just the right amount’, ‘more than necessary’.
4. Do your professional caregivers give you conflicting information? Answer options: ‘never’, ‘sometimes’, ‘usually’, ‘always’.
5. Do your professional carers explain things to you understandably? Answer options: ‘never, ‘sometimes’, ‘usually’, ‘always’.
6. Can you co-decide about your care? Answer options: ‘never’, ‘sometimes’, ‘usually’.
7. Do your carers take your personal wishes into account? Answer options: ‘none of them do’, ‘some of them do’, ‘most of them do’, ‘all of them do’.

And to relatives of the deceased:

1. Did you receive information about your relative’s condition? Answer options: ‘less than necessary’, ‘just the right amount’, ‘more than necessary’.
2. Did you get information about the pros and cons of different treatments? Answer options: ‘less than necessary’, ‘just the right amount’, ‘more than necessary’.
3. Did you get information about the impending death? Answer options: ‘less than necessary’, ‘just the right amount’, ‘more than necessary’.

These items were mainly derived from the CQ-index Palliative Care, a structured questionnaire developed by Claessen et al.[29,30] containing questions on care experiences and consisting of a patient version and a relative version. The questionnaires were eventually tested in a pilot study among patients and relatives. Details of the questionnaires and measurement procedure can be found elsewhere.[26-28]

Statistical analyses

Descriptive statistics on the evaluations of information provision are presented for people with cancer who were supported by PCSs as well as for relatives of those who had died while under the care of PCSs, according to different patient characteristics. To control simultaneously for the effect of patient characteristics (age, gender, length of guidance, and/or type of PCS, depending on the model), multivariable logistic regression models were used. Statistical significance was set at $p<.05$. All statistical analyses were performed in IBM SPSS Statistics version 23.0.

Ethics

At inclusion, all respondents received a questionnaire and a covering letter (including a request for informed consent) providing information about the purpose and the voluntary character of participation in the study. Since the palliative care teams were responsible for the distribution of questionnaires and anonymous numbers were used for each participant, the completed questionnaires received by the researchers could never be linked to the identifying information and anonymity was preserved at all times. The protocol of the entire measurement procedure and data collection was approved by the Ethical Review Board of Brussels University Hospital of the Vrije Universiteit Brussel (VUB) and by the local ethical board of every hospital participating in the measurement.

5.3 RESULTS

Characteristics of the study population

The participating 34 specialist palliative care teams identified a total of 784 eligible people with cancer being guided by PCSs at the time of the measurement and 1,795 who had died while under the guidance of PCSs between the previous four weeks and four months (*Table 1*). A questionnaire was received from 628 cancer patients (response rate 80%) of those supported by PCSs at the time of the measurement and from 980 relatives of deceased patients (response rate 55%). In both groups the majority of patients were between 65 and 84 years old (58.9% and 59.9%) and the gender distribution was fairly equal (male: 49.7% and 54.2%).

Information provision as evaluated by all responses taken together

Overall, about 80% of people with cancer being guided by PCSs at the time reported having received just the right amount of information about their diagnosis and the course of their disease (*Table 2*). Around 73% reported that they had received just the right amount of information about end-of-life care. The majority (82.6%) indicated that they had never been given conflicting information and that things had always been explained understandably (63.5%). More than half stated that they were always given the opportunity to take part in decisions about their care, and most (66.6%) reported that all of their professional caregivers took their personal wishes into account.

Approximately three-quarters of bereaved relatives reported that they had received just the right amount of information about the person’s condition, the pros and cons of different treatments and the impending death (*Table 2*).

Information provision as evaluated by people with cancer and bereaved relatives according to age and gender

Adjusted for gender, length of guidance and type of PCS, those aged 18-64 years were more likely than those aged 65-84 to have sometimes received conflicting information (OR=1.79; 95% CI=1.05-3.06), but less likely to have been given the opportunity to co-decide about their care never or only sometimes (OR=.43; 95% CI=.20-.89) (*Table 3*). Compared with those aged 65-84 years, those aged 85 years and older were more likely to have had none or only some of their carers take their personal wishes into account (OR=3.30; 95% CI=1.15-9.46). Gender was not significantly associated with any of the items on patients’ evaluation of information provision, participation in decision-making about care and the extent to which personal wishes are taken into account.

Table 1. Characteristics of the study population

	Response rate over four measurement periods	
	Study population 1	**Study population 2**
	People with cancer being guided by PCSs at the time of the measurement	People with cancer who had died while under the care of PCSs four weeks to four months ago
Eligible, *n*	784	1795
Patient or relative questionnaire received, *n* (%)	628 (80%)	980 (55%)
	Characteristics of patients enrolled in the study over four measurement periods	
	Study population 1	**Study population 2**
	People with cancer being guided by PCSs at the time of the measurement[±]	People with cancer who had died while under the care of PCSs four weeks to four months ago[±]
Age, *n* (%)		
18-64 years	189 (30.1)	207 (21.7)
65-84 years	370 (58.9)	571 (59.9)
≥ 85 years	69 (11.0)	175 (18.4)
Gender, *n* (%)		
Male	312 (49.7)	531 (54.2)
Female	313 (49.8)	449 (45.8)
Length of guidance, *n* (%)		
< 7 days	151 (24.0)	344 (35.1)
7-28 days	169 (26.9)	396 (40.4)
> 28 days	255 (40.6)	239 (24.4)
Type of PCS, *n* (%)		
Multidisciplinary mobile palliative homecare team	73 (11.6)	62 (6.3)
Hospital-based palliative care unit	309 (49.2)	663 (67.7)
Hospital-based mobile palliative support team	246 (39.2)	255 (26.0)

Abbreviations: PCS(s), specialist palliative care service(s).

Percentages are column percentages.

[±] Values may not add up to the total due to missing data. Missing values <5% for all variables, except for 'length of guidance' in study population 1 (*n*=53, 8.4%).

Adjusted for the effects of the other variables, relatives of those who had died aged 18-64 years were more likely to have received less information than necessary about the patient's condition (OR=1.74; 95% CI=1.06-2.84) and the pros and cons of different treatments (OR=1.63; 95% CI=1.03-2.60) than relatives of those aged 65-84 years (*Table 3*). Relatives of female patients were less likely to have received more than necessary information about the patient's condition than relatives of male patients (OR=.52; 95% CI=.34-.79).

Information provision as evaluated by people with cancer and bereaved relatives according to length of guidance and type of palliative care service

Adjusted for age, gender and type of PCS, those who had received guidance by PCSs for 29 days or longer were more likely to have had most of their carers taking their personal wishes into account than were those who had been guided for less than seven days (OR=1.74; 95% CI=1.04-2.91). None of the other items were significantly associated with the length of guidance (*Table 3*).

Compared with those receiving care within a hospital-based palliative care unit, those supported by a hospital-based mobile palliative support team were more likely to have received less information than they considered necessary about end-of-life care (OR=2.33; 95% CI=1.31-4.15), to have received conflicting information (OR=2.45; 95% CI=1.38-4.35), not always to have had things explained understandably to them (OR=2.08; 95% CI=1.38-3.13), not always to have been given the opportunity to co-decide about their care (OR=2.05; 95% CI=1.37-3.08), and not to have had all of their caregivers take their wishes into account (OR=3.77; 95% CI=2.45-5.80). Those receiving care from a multidisciplinary mobile homecare team were more likely to have had none or only some of their caregivers take their wishes into account compared with those receiving care within a palliative care unit (OR=5.92; 95% CI=1.25-28.00).

The length of guidance by PCSs was not associated with any of the items on evaluation of information provision by relatives (*Table 3*). Compared with relatives of people who had died while under the guidance of a palliative care unit, relatives of those who had received care from a mobile palliative support team were more likely to have received less information than they considered necessary about the person's condition (OR=3.25; 95% CI=2.08-5.08), about the pros and cons of different treatments (OR=3.23; 95% CI=2.12-4.93) and about the impending death (OR=2.95; 95% CI=1.92-4.54) and were less likely to have received more than necessary information about the impending death (OR=.52; 95% CI=.29-.96). Relatives of those who had received care from a mobile homecare team were more likely to have received more information than they considered necessary about the person's condition than relatives of those who had died while under the guidance of a palliative care unit (OR=2.16; 95% CI=1.10-4.21) and either less or more than necessary (OR=5.28; 95% CI=2.53-11.00 and OR=3.37; 95% CI=1.65-6.85) about the imminent death of their relative.

Table 2. Information provision as evaluated by people with cancer being guided by PCSs at the time of the measurement (study population 1) and relatives of people with cancer who had died while under the care of PCSs (study population 2).

Study population 1			
People with cancer being guided by PCSs at the time (*n*=628)±			
	Less than necessary	**Just the right amount**	**More than necessary**
	n (%)	*n* (%)	*n* (%)
Information about diagnosis	43 (7.3)	480 (81.5)	66 (11.2)
Information about course of disease	70 (12.4)	449 (79.8)	44 (7.8)
Information about end-of-life care	79 (14.9)	367 (73.2)	63 (11.9)
	Never	Sometimes	Usually/always*
	n (%)	*n* (%)	*n* (%)
Conflicting information provided	502 (82.6)	81 (13.3)	25 (4.1)
	Never/sometimes*	**Usually**	**Always**
	n (%)	*n* (%)	*n* (%)
Things are explained understandably	31 (5.1)	193 (31.5)	389 (63.5)
Patient can co-decide about care	68 (11.2)	212 (35.0)	326 (53.8)
	None of them do/ some of them do*	**Most of them do**	**All of them do**
	n (%)	*n* (%)	*n* (%)
Carers take patient's personal wishes into account	28 (4.6)	176 (28.8)	407 (66.6)
Study population 2			
Relatives of people with cancer who had died while under the care of PCSs (*n*=980)±			
	Less than necessary	**Just the right amount**	**More than necessary**
	n (%)	*n* (%)	*n* (%)
Information about patient's condition	104 (10.7)	742 (76.5)	124 (12.8)
Information about pros and cons of different treatments	119 (12.6)	719 (76.1)	107 (11.3)
Information about impending death	123 (13.2)	699 (74.9)	111 (11.9)

Abbreviations: PCS(s), specialist palliative care service(s).

Percentages are row percentages.

* Categories were combined because of small group sizes.

± Values may not add up to the total due to missing data. Missing values <5% for all variables, except for 'information about course of disease' in study population 1 (*n*=65, 10.4%), 'information about end-of-life care' in study population 1 (*n*=99, 15.8%), and 'information about impending death' in study population 2 (*n*=85, 14.8%).

Table 3. Information provision as evaluated by people with cancer being guided by PCSs at the time of the measurement (study population 1) and relatives of people with cancer who had died while under the care of PCSs (study population 2) according to age, gender, length of guidance and type of PCS.

	Age	
	18-64 years (vs. 65-84 years)	≥ 85 years (vs. 65-84 years)
	OR (95% CI)†	OR (95% CI)†
Study population 1		
People with cancer being guided by PCSs at the time (*n*=628)		
Information about diagnosis (ref cat=just the right amount)		
Less than necessary	.73 (.33-1.62)	1.47 (.56-3.87)
More than necessary	1.23 (.68-2.21)	.35 (.08-1.50)
Information about course of disease (ref cat=just the right amount)		
Less than necessary	1.02 (.55-1.86)	1.78 (.80-3.96)
More than necessary	1.19 (.57-2.48)	.62 (.14-2.82)
Information about end-of-life care (ref cat=just the right amount)		
Less than necessary	.96 (.54-1.73)	1.26(.53-3.00)
More than necessary	1.30 (.69-2.45)	1.46 (.55-3.85)
Conflicting information provided (ref cat=never)		
Sometimes	**1.79 (1.05-3.06)**	1.52 (.65-3.55)
Usually/always*	.62 (.22-1.74)	.35 (.05-2.75)
Things are explained understandably (ref cat=always)		
Never/sometimes*	.85 (.35-2.05)	1.82 (.56-5.93)
Usually	.74 (.48-1.14)	1.69 (.93-3.07)
Patient can co-decide about care (ref cat = always)		
Never/sometimes*	**.43 (.20-.89)**	1.21 (.49-3.01)
Usually	.79 (.52-1.20)	.89 (.47-1.67)
Carers take patient's personal wishes into account (ref cat=all of them do)		
None of them do/some of them do*	.62 (.20-1.98)	**3.30 (1.15-9.46)**
Most of them do	1.51 (.99-2.31)	.64 (.29-1.40)
Study population 2		
Relatives of people with cancer who had died under the care of PCSs (*n*=980) (*n*=980)		
Information about patient's condition (ref cat=just the right amount)		
Less than necessary	**1.74 (1.06-2.84)**	1.06 (.59-1.92)
More than necessary	.99 (.61-1.62)	.91 (.53-1.56)

Gender	Length of guidance		Type of PCS	
Female (vs. male)	7-28 days (vs. > 7 days)	≥ 29 days (vs. > 7 days)	Multidisciplinary mobile palliative homecare team (vs. hospital-based palliative care unit)	Hospital-based mobile palliative support team (vs. hospital-based palliative care unit)
OR (95% CI)[‡]	OR (95% CI)[§]	OR (95% CI)[§]	OR (95% CI)[¥]	OR (95% CI)[*]
.93 (.48-1.81)	1.26 (.52-3.07)	1.11 (.46-2.69)	1.13 (.33-3.81)	1.33 (.65-2.72)
.95 (.54-1.66)	.97 (.46-2.07)	.85 (.41-1.75)	1.56 (.63-3.83)	.96 (.51-1.79)
1.30 (.75-2.24)	1.29 (.61-2.73)	1.34 (.65-2.78)	1.39 (.57-3.36)	1.10 (.61-1.99)
.83 (.42-1.65)	.42 (.16-1.07)	.50 (.22-1.12)	1.57 (.50-4.99)	1.23 (.58-2.60)
1.50 (.88-2.55)	1.03 (.51-2.08)	.91 (.46-1.77)	2.08 (.84-5.16)	**2.33 (1.31-4.15)**
.98 (.54-1.75)	.89 (.40-1.98)	.94 (.45-1.98)	1.70 (.66-4.40)	1.34 (.71-2.56)
.77 (.46-1.27)	1.11 (.53-2.32)	1.42 (.73-2.79)	1.99 (.87-4.54)	**2.45 (1.38-4.35)**
.75 (.32-1.77)	.81 (.26-2.48)	.88 (.30-2.56)	1.25 (.30-5.31)	1.30 (.51-3.31)
.99 (.46-2.15)	.98 (.35-2.76)	.86 (.32-2.31)	2.95 (.84-1.40)	**2.95 (1.22-7.13)**
.85(.59-1.24)	1.48(.89-2.48)	1.56 (.95-2.56)	1.28 (.68-2.44)	**2.08 (1.38-3.13)**
1.83 (1.00-3.35)	1.08 (.48-2.42)	1.18 (.56-2.52)	1.75 (.58-5.29)	**6.66 (3.28-13.52)**
.96 (.66-1.40)	1.31 (.80-2.16)	1.58 (.97-2.57)	**.50 (.25-.98)**	**2.05 (1.37-3.08)**
1.44 (.60-3.41)	2.11 (.60-7.41)	1.75 (.51-6.05)	**5.92 (1.25-28.00)**	**1.70 (3.37-33.91)**
.96(.64-1.42)	1.33 (.76-2.31)	**1.74 (1.04-2.91)**	1.16 (.58-2.31)	**3.77 (2.45-5.80)**
.83 (.54-1.27)	1.04 (.63-1.71)	.93 (.53-1.63)	1.33 (.49-3.61)	**3.25 (2.08-5.08)**
.52 (.34-.79)	1.25 (.79-1.96)	.99 (.57-1.72)	**2.16 (1.10-4.21)**	.88 (.53-1.45)

Table 3. Continued

	Age	
	18-64 years (vs. 65-84 years)	≥ 85 years (vs. 65-84 years)
	OR (95% CI)[†]	OR (95% CI)[†]
Information about pros and cons of different treatments (ref cat=just the right amount)		
Less than necessary	**1.63 (1.03-2.60)**	.94 (.53-1.67)
More than necessary	.77 (.45-1.32)	.72 (.40-1.31)
Information about impending death (ref cat=just the right amount)		
Less than necessary	1.28 (.80-2.03)	.57 (.30 -1.07)
More than necessary	.99 (.59-1.64)	.68 (.37-1.27)

Abbreviations: PCS(s), specialist palliative care service(s).

[†] Multivariable analyses were conducted using a multinomial logistic regression enter model adjusted for gender, length of guidance, and type of PCS.

[‡] Multivariable analyses were conducted using a multinomial logistic regression enter model adjusted for age, length of guidance, and type of PCS.

Gender	Length of guidance		Type of PCS	
Female (vs. male)	7-28 days (vs. > 7 days)	≥ 29 days (vs. > 7 days)	Multidisciplinary mobile palliative homecare team (vs. hospital-based palliative care unit)	Hospital-based mobile palliative support team (vs. hospital-based palliative care unit)
OR (95% CI)‡	OR (95% CI)§	OR (95% CI)§	OR (95% CI)¥	OR (95% CI)*
1.14 (.76-1.71)	1.17 (.73-1.86)	.91 (.53-1.58)	.86 (.29-2.54)	**3.23 (2.12-4.93)**
1.04 (.68-1.57)	1.05 (.65-1.72)	1.19 (.68-2.08)	1.55 (.74-3.25)	.71 (.41-1.23)
.77 (.52-1.16)	1.06 (.67-1.70)	.99 (.58-1.68)	**5.28 (2.53-11.00)**	**2.95 (1.92-4.54)**
.64 (.42-.99)	1.64 (.99-2.74)	1.70 (.94-3.07)	**3.37 (1.65-6.85)**	**.52 (.29-.96)**

§ Multivariable analyses were conducted using a multinomial logistic regression enter model adjusted for age, gender, and type of PCS.

¥ Multivariable analyses were conducted using a multinomial logistic regression enter model adjusted for age, gender, and length of guidance.

* Categories were combined because of small group sizes.

5.4 DISCUSSION AND CONCLUSION

Discussion

This study found that the majority of the people with cancer being guided by specialist palliative care services (PCSs) and relatives of patients who had died while under the care of PCSs reported having received the right amount of information about the illness and care. The type of PCS was associated with their perceptions of information provision. Information provision seemed to have been more satisfactory to both the patients and the bereaved in the case of separate hospital-based palliative care units than in the case of specialist palliative care teams offering support and advice to other healthcare professionals.

People with cancer using PCSs overall gave a positive evaluation of the information they received about their illness and about their end-of-life care, about the extent to which their wishes were respected by professional caregivers and about the possibility of participating in decision-making about their care. Bereaved relatives' evaluations were also positive regarding the information received about the illness, care and impending death. Previous studies have indicated that information provision is a frequently reported unmet need among people with cancer in general[31] and that information about palliative care, even in the more advanced stages of the illness, is often not provided.[32] Based on the ethical principle of respect for autonomy, patients must be given the information desired and needed to understand their medical condition, treatment options and probable outcomes.[33] In Belgium, the patient's right to be informed – but also the right not to be informed on his/her explicit request – is one of the main principles prescribed by the Act on Patients' Rights which came into force in 2002.[34] Our study seems to suggest that information needs are more often met in a context of specialist palliative care. These services are well positioned to respond to personal needs because of their emphasis on providing individually tailored care and facilitating informed decisions in the context of the preferences of the person with advanced cancer and those close to them and enhanced communication between them and their professional caregivers.[4,35,36]

A striking result of our study was the strong association between information provision and the type of PCS. Information provision was evaluated more positively by both those with cancer and the bereaved relatives where care was provided within a hospital-based palliative care unit in comparison with a hospital-based mobile palliative support team or a multidisciplinary mobile palliative homecare team. In order to understand these results, we need to consider the difference between the services available in Belgium. Mobile palliative homecare teams consist of nurses, a physician, an administrative assistant and possibly other disciplines such as a psychologist. Their role is to assist other professional caregivers in the homecare setting on matters of palliative care where the care itself remains the responsibility of these others. Mobile palliative support teams in hospitals consist at minimum of a physician (0.5 full-time equivalent), a nurse (0.5 full-time equivalent) and a psychologist (0.5 full-time equivalent) for every 500 hospital beds. Their role is also to advise and assist physicians and nurses in different hospital wards without replacing them. Just like the homecare teams, they deliver second-line support. Hospital-based palliative care units, however, are able to deliver care 24 hours, seven days a week as a last resort, for people in the palliative phase for whom no other care solution is possible. The team comprises a minimum of 1.5 full-time equivalent nurses per bed and can call on physiotherapists, social workers, spiritual/existential consultants, psychologists and psychiatrists. A palliative care unit is usually small, with at least six and at most 12 beds, and allows visits 24 hours a day.[34] These circumstances make a very high level of personalized care possible, which could explain why evaluations of information provision were particularly high in this group. Compared with this level of provision, multidisciplinary mobile palliative homecare teams and hospital support teams have a smaller window of opportunity to have a direct impact on care.

Another finding was that the patient's age, but not gender, influenced evaluations of decision-making. Older people with cancer were more likely to have had a less active role in making decisions about their care and felt that their personal wishes were not always taken into account. It has been suggested that older patients tend to prefer a less active role in medical decision-making, an assumption that may lead to inequity in healthcare provision.[37] Research has also indicated that older patients generally receive less information from physicians than do younger patients, although they do not have lower informational needs.[38] It should not automatically be assumed that older people desire less information or participation. Everyone, regardless of age, should be invited to state what role they want to play in decisions about their care[39] and the decision-making process should be adapted according to their preferences.[40]

Relatives of younger adult patients (18-64 years) more often reported having received less information than they considered necessary about the person's condition and treatment than relatives of those aged 65-84 years. While no socio-demographic data on relatives were collected within this study, the 'most important relatives' of patients were predominantly partners whom, it is fair to assume, will be of a similar age. It is possible that younger relatives were less satisfied with the amount of information received compared to their older counterparts – which corroborates previous findings[41] – because they had higher expectations or were more assertive in their communication.

As far as we are aware, this study is the first to show differences between types of PCSs regarding information provision about the illness and end-of-life care as evaluated by both patients and bereaved relatives. However, a few limitations must be considered. One limitation is that that the survey asked the respondents whether they had received the right amount of information about the described topics, but did not ask whether they were satisfied with the content, detail and timing of the information. Another limitation concerns the study design. The cross-sectional nature did not allow us to examine changes over time. Alterations in disease status may affect a patient's preferences for information and involvement in decision-making,[42] and therefore future studies would benefit from the availability of data at different time points along the illness trajectory. Furthermore, it is important to mention that the data was collected through self-reports. Although we believe that our focus on the perceptions of patients and relatives is a strength, especially in light of the emphasis within palliative care on providing care tailored to individual needs, this approach has some disadvantages. Self-reported measures are vulnerable to recall and reporting biases. It is not clear from this survey study how much information was actually provided. A final shortcoming of the present study is that different questionnaire items were used for the two populations studied, making it impossible to directly compare patient responses with those from relatives. More research is needed to clarify whether and to what degree perceptions of information provision by palliative care services differ between cancer patients and those close to them.

Conclusion

Although prior research has indicated that information provision is often considered suboptimal among people with advanced cancer, this study adds to the growing literature on the benefits of PCSs by showing that the experience of information provision of people with cancer and bereaved relatives is rated mainly positively in this context in Belgium. These services are well suited to providing people with information and support adapted to the individual and family requirements. Nevertheless, we found substantial differences between different types of PCSs, and some smaller differences across different age and gender groups.

Practice implications

As the population ages, the number of people dying of cancer continues to rise, and healthcare systems need to be adequately prepared to adapt their services in a context of increasing demand for palliative care. Understanding patients' and relatives' perceptions of the care received from PCSs is important for identifying areas for improvement. The results of the present study may help optimize information provision and decision-making in oncology within the different palliative care structures and could also inform other countries currently in the process of improving their palliative care regulations and policies.

An important finding was that both patients and bereaved relatives tended to evaluate information provision more favorably if they had received continuous care within a separate palliative care unit in the hospital than if they had been supported by palliative care teams mainly acting as consultants, providing support or advice at the request of other healthcare professionals. Although the structure and environment of a palliative care unit seems ideal for fostering a culture of adapted and flexible care, which increases the likelihood of achieving optimal information provision and involvement in decision-making, this level of provision is time and resource intensive. Due to staffing and resource constraints, it is likely that methods used within palliative care units are not always easily transferable to other settings. Ongoing education and training addressed to policy makers, healthcare professionals, patients and families should be encouraged to help build an optimal palliative care culture focusing on direct versus indirect involvement where possible. Further research is needed to clarify which aspects of specialist care service provision in oncology are most associated with effective information provision and decision-making, and how services can learn from each other's best practices.

ADDITIONAL INFORMATION

Acknowledgements

The authors would like to thank all participating specialist palliative care services for providing the data. The authors also would like to thank Jane Ruthven for her linguistic help.

Author's contributions

K.L., L.V.d.B., L.D. and J.C. contributed to the study concept, design and data acquisition. M.N.V. and K.L. contributed to the statistical analysis. M.N.V. drafted the manuscript with input from all authors. All authors contributed to the interpretation of the results and approved the final manuscript. L.D. and J.C. contributed equally as last author.

Role of funding source

This study was realized with the support of Kom op tegen Kanker (KOTK), a campaign of the Flemish League Against Cancer. The first author, M.N.V., has received funding from the European Union's Seventh Framework Programme FP7/2007-2013 (grant agreement no. 602541).

Conflict of interest

The authors declare that there is no conflict of interest.

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Part III

End-of-life decisions and the preceding decision-making process in people who died from cancer

6

End-of-life decision-making across cancer types: results from a nationwide retrospective survey among treating physicians

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This chapter is also published as an article in: *British Journal of Cancer* 2018; **118**(10): 1369-76. [2018 SCI impact factor 5.416; journal ranking Q1; ranking n° 44 of 230 in ONCOLOGY]

ABSTRACT

Background: The treatment of advanced cancer often involves potentially life-shortening end-of-life decisions (ELDs). This study aimed to examine the prevalence and characteristics of ELDs in different cancer types.

Methods: A nationwide death certificate study was conducted based on a large random sample of all deaths in Flanders, Belgium, between 1 January and 30 June 2013. All cancer deaths were selected (*n*=2,392). Attending physicians were sent a questionnaire about ELDs and the preceding decision-making process.

Results: The response rate was 58.3%. Across cancer types, a non-treatment decision occurred in 7.6-14.0%, intensified pain and symptom alleviation in 37.5-41.7%, euthanasia or physician-assisted suicide in 8.7-12.6%, and life shortening without explicit patient request in 1.0-3.4%. ELD prevalence did not differ significantly by cancer type. Reasons for ELDs were most frequently patient's physical suffering and lack of prospect of improvement. 'Anticipated further suffering' and 'unbearable situation for relatives' were reasons more often reported in hematological cancer than in other cancer types. Patient, family and caregiver involvement in decision-making did not differ across cancer types.

Conclusion: Euthanasia or physician-assisted suicide rates were relatively high in all cancer types. Neither the prevalence of ELDs nor characteristics of the decision-making process differed substantially between cancer types. This indicates a uniform approach to end-of-life care, including palliative care, across oncological settings.

6.1 INTRODUCTION

Many people with advanced cancer face difficult treatment decisions at the end of life. In responding to these decisions, patients need to balance the realistic possibilities of prolonging life by continuing treatment or starting new treatments on the one hand, against comfort and quality of life on the other hand.[1] As a result, it can happen that decisions are made that may potentially hasten the patient's death. This can be a foreseen but unintended consequence or an intended outcome. These end-of-life decisions with a possible or certain life-shortening effect (ELDs), on which this article particularly focuses, include non-treatment decisions (withholding or withdrawing of potentially life-sustaining treatment), intensifying pain or symptom alleviation (increasing pain or symptom relief by administering high-dose drugs while taking into account the possibility or certainty that this could hasten death), and administering drugs with the explicit intention of hastening death (euthanasia, physician-assisted suicide, or life shortening without the individual's explicit request). Although euthanasia and physician-assisted suicide are still illegal in most countries, a growing number of countries now have legislation allowing one or both of these practices (Belgium, the Netherlands, Luxembourg, Colombia, Canada, five US states and Switzerland).[2]

Previous research has shown that ELDs, specifically intensified symptom alleviation, euthanasia and physician-assisted suicide, are more frequent in people dying from cancer than in people dying from other conditions.[3-6] Possible explanations may be that symptom burden is higher in cancer than in other diseases[7,8] and that palliative care services – specializing in symptom management – are more readily available or accessible.[9-12] Moreover, there is a trend in cancer care towards earlier diagnosis and open doctor-patient communication about the prognosis,[13] which may lead to more ELDs.

Previous studies have described ELDs in cancer patients.[3,5,14,15] Unfortunately, none have examined the prevalence of ELDs and characteristics of the decision-making process in different cancer types, although this could be valuable for several reasons. Equity of care aims to ensure that the quality of end-of-life care provided does not differ by characteristics unrelated to a patient's needs.[16] We know, however, from previous studies that people with different types of cancer may receive different types and intensity of end-of-life care, which may for example be related to differences in symptoms or trajectories of functional decline at the end of life.[17-20] Patients with hematological cancer in particular tend to have poorer access to palliative care services, are more likely to be admitted to an intensive care unit and to receive aggressive end-of-life care, and are less likely to die at home than those with solid malignancies.[20,21-28] Such variations across cancer types, which could point to potential inequities in the provision end-of-life care to people with advanced cancer, may also exist regarding the occurrence of ELDs and characteristics of decision-making, e.g., the extent to which physicians involve patients and their families in this process.

Understanding the relationship between cancer type and end-of-life decision-making could help inform policy and practice about whether tailoring terminal care to specific cancer diagnoses is needed. The aim of this study is to examine the prevalence of ELDs and the characteristics of the decision-making process in people dying from different cancer types in 2013 in Flanders, Belgium, a country where euthanasia has been legal under specific conditions since 2002.

The specific research questions are:

1. What is the prevalence of different types of ELDs across cancer types?
2. What are physicians' reasons for making ELDs across cancer types?
3. To what extent are patients and families involved in the decision-making process across cancer types?
4. To what extent are professional caregivers involved in the decision-making process across cancer types?

6.2 PATIENTS AND METHODS

Study design

A death certificate study was conducted, based on a representative sample of deaths in Flanders, Belgium. The Flemish Agency for Care and Health (FACH) selected a random sample of all deaths of Belgian residents (aged one year and above) between 1 January and 30 June 2013, stratified for the likelihood of an ELD being made. Larger samples were taken for strata in which the cause of death, as indicated on the death certificate, made an ELD more likely.[29] This resulted in a total sample of 6,871. For this analysis, all deaths in the database with an underlying cause of cancer were selected (*n*=2,669).

Certifying physicians were sent a four-page questionnaire via standard mail within two months of the death concerning medical decisions made at the end of life, the decision-making process, and the care provided. They were requested to complete the questionnaire by consulting the patient's medical file. If the certifying physician was not the treating physician, the questionnaire was passed on to the treating physician. A lawyer acting as intermediary between responding physicians, researchers and the FACH ensured 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-respondents asking their reasons for not participating. The mailing and anonymity procedures 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. The study design, sampling, and mailing procedure are described in detail elsewhere.[29,30]

Questionnaire

The questionnaire, tested thoroughly by a panel of physicians, was largely identical to those of previous studies in Belgium, the Netherlands and other European countries, the first of which had been developed for the 1990 Dutch survey on ELDs.[31] In a validation study, the classification of ELDs that was based on the responses given on the postal survey matched the classification that was based on the responses given in face-to-face interviews.[32] The questionnaire first asked whether death had been sudden and unexpected and whether the attending physician's first contact with the patient had been after death. If the answer to both these questions was no – hence end-of-life decision-making before death was not precluded – they were then asked whether they had (1) withheld or withdrawn life-prolonging medical treatment (e.g., chemotherapy, artificial provision of nutrition and hydration, provision of antibiotics, mechanical ventilation) taking into account or explicitly intending the hastening of death (non-treatment decision); (2) intensified the alleviation of pain and/or other symptoms with drugs with the possibility of hastening death (intensified alleviation of pain and symptoms) or (3) administered, supplied or prescribed drugs with the explicit intention of hastening death. If in the latter case someone other than the patient at the patient's explicit request had administered the drugs, the act was classified as euthanasia; if drugs had been prescribed or supplied and self-administered, the act was classified as physician-assisted suicide. If there had been no explicit request from the patient, the act was classified as life abbreviation without explicit patient request. For patients for whom more than one ELD was made, the act with the most explicit life-shortening intention was regarded as the most important ELD. When two decisions with similar life-shortening intention were made, administering drugs was regarded as prevailing over withholding or withdrawing treatment as the most important ELD. Questions then followed about the reasons for the most important ELD and about the decision-making process (the involvement of the patient, family, and professional caregivers in making the decision).

Data on sex, age, place and underlying cause of death were available from the individually linked death certificate information. The underlying cause of death variable was coded according to ICD-10. People dying from cancer were identified according to ICD-10 codes C00 to C97: gastrointestinal (C15-26), respiratory (C30-39, C45-49), genitourinary (C51-58, C60-63, C64-68), breast (C50), head and neck (C00-C14), hematological (C81-96), and 'other' for other types of cancer. These included bone and articular cartilage (C40-41); skin (C43-44); eye, brain and central nervous system (C69-72); thyroid and endocrine glands (C73-75); ill-defined, secondary and unspecified sites (C76-80); and independent (primary) multiple sites (C97).

Statistical analysis

The subset of cancer-related deaths was weighted 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 were only needed for place of death). After this weighting procedure there were no significant differences between the sampled cancer deaths and all cancer deaths on any of these variables.

Descriptive statistics on prevalence of ELDs, types of ELDs, reasons for the ELD, and the involvement of the patient, family, and professional caregivers in the decision-making process are presented for different cancer types. Results for euthanasia and physician-assisted suicide were combined because the latter only occurred in five cases. Deaths from head and neck cancer (n=41) were combined with the 'other' category (n=131) because of its small group size. Bivariate cross-tabulations and multivariable logistic regression models were calculated to compare patients dying from different cancer types, with statistical significance set at $p<.05$. Bivariate differences between cancer types were calculated using Pearson chi-square tests. Multivariable regression models incorporated the most important confounders to determine the independent effect of cancer type on ELDs and the preceding decision-making process. All statistical analyses were performed with complex samples functions in IBM SPSS Statistics version 23.0.

6.3 RESULTS

Questionnaires were returned for 1,394 of 2,669 deaths. Non-response questionnaires revealed that responding was impossible in 277 cases, e.g., 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 differed significantly in age at death, sex, living situation, marital status, and place of death *(Table 1)*.

Prevalence of end-of-life decisions across cancer types

Of all cancer deaths, 22.6% were judged to be sudden and unexpected, and 66.1% were preceded by an end-of-life decision, ranging from 60.9% in breast cancer to 69.4% in respiratory cancer (*Table 2*). A non-treatment decision was made in 7.6% (breast) to 14.0% (respiratory), intensified alleviation of pain and symptoms in 37.5% (hematological) to 44.0% (other). Euthanasia or physician-assisted suicide occurred in 8.7% (genitourinary) to 12.6% (respiratory), and life abbreviation without the explicit request from the patient in 1.0% (respiratory) to 3.4% (genitourinary).

The proportion of deaths in which an ELD was made did not differ significantly between cancer types. Also, no significant differences in the occurrence of specific ELDs were found. These associations remained non-significant in multivariable regression models adjusting for age, sex, marital status, and place of death (results not shown).

Table 1. Characteristics of patients dying from cancer in 2013 in Flanders, Belgium (*n*=1394)

	Cancer type		
	All cancer deaths (*n*=1,394)	**Gastrointestinal (*n*=417)**	**Respiratory (*n*=334)**
Characteristics	Weighted % [b]		
Age at death, years			
1-64	24.1	21.4	31.1
65-79	41.0	42.4	45.9
≥ 80	34.9	36.2	22.9
Sex			
Male	57.1	57.9	71.0
Female	42.9	42.1	29.0
Living situation			
Alone	22.2	21.1	21.3
In household with others	66.2	68.9	70.8
Institution	11.6	9.9	7.9
Marital status			
Single	8.2	9.7	8.6
Married	55.1	55.3	60.1
Widowed	26.9	27.6	17.5
Divorced	9.8	7.4	13.8
Place of death			
At home	30.6	29.7	36.0
Hospital	58.0	59.2	57.3
Care home	11.5	11.2	6.7
Treating physician			
Clinical specialist	55.4	54.5	56.9
General practitioner	44.6	45.5	43.1

Percentages are column percentages. Not included in table and analyses: ‘other’ category for *living situation* *n*=5 (0.4% of all cancer deaths); missing data for *living situation* *n*=10 (0.7% of all cancer deaths); ‘unknown’ category for *marital status* *n*=4 (0.3% of all cancer deaths); ‘other’ category for *place of death* *n*=34 (2.4% of all cancer deaths); missing data for *place of death* *n*=1 (0.1% of all non-sudden cancer deaths); ‘other’ category for *physician specialty* *n*=61 (4.4% of all cancer deaths); missing data for *physician specialty* *n*=18 (1.3% of all cancer deaths).

Cancer type				
Genitourinary (*n*=252)	Breast (*n*=113)	Haematological (*n*=106)	Other [a] (*n*=172)	
Weighted % [b]				*P*-value [c]
10.0	31.5	16.6	37.2	**<.001**
41.9	42.3	29.6	33.4	
48.1	26.2	53.8	29.4	
60.3	0.0	62.7	58.3	**<.001**
39.7	100.0	37.3	41.7	
25.1	22.6	26.3	18.9	**.025**
60.9	60.4	54.9	70.2	
14.0	16.9	18.8	10.9	
4.1	6.1	9.7	10.4	**.001**
56.8	49.5	43.8	53.9	
30.3	37.6	37.8	24.1	
8.8	6.9	8.7	11.6	
29.9	26.3	19.2	33.7	**.002**
54.2	56.9	66.3	56.7	
15.8	16.8	14.5	9.7	
51.8	53.1	65.6	54.6	.310
48.2	46.9	34.4	45.4	

[a] 'Other' category includes head and neck; bone and articular cartilage; skin; eye, brain and central nervous system; thyroid and endocrine glands; ill-defined, secondary and unspecified sites; independent (primary) multiple sites.

[b] Percentages are weighted for the disproportionate stratification and differences in the distribution of mortality characteristics between the response sample and all patient deaths.

[c] Bivariate differences between patients with different cancer types are calculated using Pearson's chi-square tests. Bold denotes significance at $p<.05$.

Table 2. Prevalence of end-of-life decisions in patients dying from cancer in 2013 in Flanders, Belgium (*n*=1394)

	ELD made or not		
	Sudden and unexpected death, no ELD made	**Non-sudden death, no ELD made**	**Non-sudden death, at least one ELD made**
Cancer type	Weighted % [b]		
All cancer deaths (*n*=1,394)	22.6	11.3	66.1
Gastrointestinal (*n*=417)	23.8	10.8	65.5
Respiratory (*n*=334)	20.0	10.6	69.4
Genitourinary (*n*=252)	24.2	8.8	67.1
Breast (*n*=113)	21.5	17.6	60.9
Haematological (*n*=106)	22.1	16.6	61.3
Other [c] (*n*=172)	23.8	9.7	66.5
P-value [d]	.868	.132	.590

Percentages are row percentages. ELD: end-of-life decision with possible or certain life-shortening effect.

[a] Five of 211 patients were cases of physician-assisted suicide.

[b] Percentages are weighted for the disproportionate stratification and differences in the distribution of mortality characteristics between the response sample and all patient deaths.

Reasons for end-of-life decisions across cancer types

The reason most often reported by physicians for the most important ELD was physical suffering, ranging from 71.0% in hematological cancer to 87.0% in breast cancer (*Table 3*). Other important reasons included a lack of prospect of improvement (60.4% other, to 78.6% hematological), the wish of the patient (40.0% other, to 46.2% respiratory), anticipated further suffering (26.0% other, to 53.8% hematological), not to prolong life needlessly (29.7% breast, to 43.5% hematological), and expected poor quality of life (23.0% other, to 46.1% hematological). In approximately a quarter of cases, reasons for making the ELD were related to the wishes of the family.

No significant differences between cancer types were found in the reasons for ELDs, except for 'expected further suffering' (p=.003), and 'expected poor quality of life' (p=.034). In multivariable regression models adjusting for age, sex, marital status, place of death, and type of ELD, only the association between cancer type and 'expected further suffering' as a reason for the ELD remained (p=.006); this reason was more often reported in hematological cancer than in gastrointestinal, genitourinary, and other types of cancer. The association between cancer type and 'unbearable situation for relatives' became statistically significant after adjustment for confounders (p=.025); this reason was more often reported in hematological compared with gastrointestinal, breast, respiratory, and genitourinary cancer (results not shown).

Type of ELD made			
Non-treatment decision	Intensified alleviation of pain or symptoms	Euthanasia or physician-assisted suicide [a]	Life abbreviation without explicit patient request
Weighted % [b]			
12.1	41.7	10.4	1.8
12.3	41.4	10.5	1.3
14.0	41.8	12.6	1.0
12.2	42.8	8.7	3.4
7.6	41.2	10.2	1.9
12.3	37.5	9.0	2.4
11.0	44.0	9.7	1.8
.724	.947	.750	.465

[c] 'Other' category includes head and neck; bone and articular cartilage; skin; eye, brain and central nervous system; thyroid and endocrine glands; ill-defined, secondary and unspecified sites; independent (primary) multiple sites.

[d] Bivariate differences between patients with different cancer types calculated using Pearson's chi-square tests.

Involvement of patients and families in the decision-making process across cancer types

At the time the ELD was made, physicians found 66.2% of all cancer patients for whom at least one ELD was made to have had capacity for decision-making *(Table 4)*. The ELD was discussed with 81.7% of patients judged to have capacity, ranging from 71.6% in genitourinary to 92.3% in hematological cancer. The ELD was made in response to an explicit patient request in 71.7% (gastrointestinal) to 82.3% (hematological) of cases where the patient was deemed to have capacity. For those lacking capacity, a written advance directive was present in 1.4% (genitourinary) to 14.4% (other) of cases, and the ELD was discussed with the family in 59.2% (other) to 74.9% (breast).

The capacity of the patient to make decisions was not related to cancer type. For those with capacity, the proportion of cases in which the ELD was discussed with them and the proportion in which the ELD was made in response to an explicit request from them did not differ by cancer type. For those without capacity, neither the presence of a living will nor the decision being discussed with the family could be related to cancer type. All these associations remained non-significant in multivariable regression (results not shown).

Table 3. Reasons for end-of-life decisions in patients dying from cancer (n=963)

	Reasons for end-of-life decision			
	Physical suffering	No prospect of improvement	Wish of the patient	Expected further suffering
Cancer type	Weighted % [a]			
All cancer deaths for which at least one ELD was made (*n*=963)	76.8	66.9	43.0	38.6
Gastrointestinal (*n*=291)	71.8	65.1	41.9	35.8
Respiratory (*n*=233)	78.9	70.0	46.2	43.4
Genitourinary (*n*=178)	79.9	62.7	40.4	34.3
Breast (*n*=71)	87.0	72.4	45.4	48.5
Haematological (*n*=68)	71.0	78.6	45.9	53.8
Other [b] (*n*=122)	77.5	60.4	40.0	26.0
P-value [c]	.115	.130	.853	**.003**

Concerns the most important ELD. ELD: end-of-life decision with possible or certain life-shortening effect. More than one reason was possible for each case. Percentages are row percentages. Not included in table and analyses: 'other' category *reasons for end-of-life decision* n=15 (1.6% of all cancer deaths for which at least one ELD was made), missing data for *reasons for reaching decision* n=77 (8.0% of all cancer deaths for which at least one ELD was made).

[a] Percentages are weighted for the disproportionate stratification and differences in the distribution of mortality characteristics between the response sample and all patient deaths.

Involvement of professional caregivers in the decision-making process across cancer types

ELDs were discussed with a colleague physician in 38.3% (breast) to 57.8% (hematological) of all cases for which at least one ELD was made (*Table 5*). A palliative care specialist was consulted in 30.7% (hematological) to 44.7% (other), and nursing staff in 35.3% (breast) to 47.9% (other). The involvement of professional caregivers in the decision-making process was not related to cancer type, and remained unchanged in multivariable regression (results not shown).

Reasons for end-of-life decision					
Life not to be prolonged needlessly	Expected poor quality of life	Wish of the family	Loss of dignity	Mental suffering	Unbearable situation for relatives
Weighted % [a]					
38.4	36.5	28.0	21.9	21.5	12.4
32.1	37.4	23.8	21.6	19.6	10.5
42.7	40.9	29.5	18.6	22.6	10.8
43.4	35.6	29.2	25.1	20.7	10.9
29.7	31.5	30.3	25.5	32.6	10.4
43.5	46.1	25.5	24.8	23.9	23.4
39.2	23.0	33.4	20.5	17.3	16.9
.098	**.034**	.559	.723	.322	.054

[b] 'Other' category includes head and neck; bone and articular cartilage; skin; eye, brain and central nervous system; thyroid and endocrine glands; ill-defined, secondary and unspecified sites; independent (primary) multiple sites.

[c] Bivariate differences between patients with different cancer types calculated using Pearson's chi-square tests. Bold denotes significance at $p<.05$.

Table 4. Involvement of patients dying from cancer and their families in the end-of-life decision-making process (*n*=963)

	Involvement of patient and family in the decision-making process			
	All cancer deaths for which at least one ELD was made		All cancer deaths for which at least one ELD was made and patient had capacity	
		Patient had capacity		Decision discussed with patient with capacity
Cancer type	*n*	Weighted % †	*n*	Weighted % [a]
All cancer deaths	963	66.2	613	81.7
Gastrointestinal	291	65.2	184	82.1
Respiratory	233	69.5	158	83.5
Genitourinary	178	63.1	109	71.6
Breast	71	69.9	44	86.9
Haematological	68	61.8	42	92.3
Other [b]	122	67.1	76	81.2
P-value [c]		.781		.069

Concerns the most important ELD. ELD: end-of-life decision with possible or certain life-shortening effect. More than one response was possible for each case. Percentages are row percentages. Not included in table and analyses: missing data for *patient had capacity n*=78 (8.1% of all cancer deaths for which at least one ELD was made), missing data for *decision discussed with patient with capacity n*=2 (0.3% of all cancer deaths for which at least one ELD was made and patient had capacity), missing data for *decision made in response to explicit request by patient with capacity n*=13 (2.1% of all cancer deaths for which at least one ELD was made and patient had capacity), missing data for *decision discussed with family of patient without capacity n*=3 (1.1% of all cancer deaths for which at least one ELD was made and patient lacked capacity).

Involvement of patient and family in the decision-making process			
All cancer deaths for which at least one ELD was made and patient had capacity	All cancer deaths for which at least one ELD was made and patient lacked capacity		
Decision made in response to explicit request by patient with capacity		Patient without capacity had written advance directive (euthanasia or other)	Decision discussed with family of patient without capacity
Weighted % [a]	*n*	Weighted % [a]	
74.2	272	5.6	64.3
71.7	82	5.7	68.5
74.6	61	5.6	61.0
73.6	56	1.4	62.5
77.1	18	5.9	74.9
82.3	21	3.1	61.1
73.7	34	14.4	59.2
.867		.179	.845

[a] Percentages are weighted for the disproportionate stratification and differences in the distribution of mortality characteristics between the response sample and all patient deaths.

[b] 'Other' category includes head and neck; bone and articular cartilage; skin; eye, brain and central nervous system; thyroid and endocrine glands; ill-defined, secondary and unspecified sites; independent (primary) multiple sites.

[c] Bivariate differences between patients with different cancer types calculated using Pearson's chi-square tests.

Table 5. Involvement of professional caregivers of patients dying with cancer in the end-of-life decision-making process (*n*=963)

	Involvement of professional caregivers in the decision-making process		
	Decision discussed with colleague physician(s)	**Decision discussed with palliative care specialist**	**Decision discussed with nursing staff**
Cancer type	Weighted % [a]		
All cancer deaths for which at least one ELD was made (*n*=963)	50.9	37.0	43.3
Gastrointestinal (*n*=291)	49.1	38.8	44.6
Respiratory (*n*=233)	53.3	33.6	43.1
Genitourinary (*n*=178)	53.1	38.4	41.0
Breast (*n*=71)	38.3	32.8	35.3
Haematological (*n*=68)	57.8	30.7	44.7
Other [b] (*n*=122)	49.8	44.6	47.9
P-value [c]	.340	.409	.741

Concerns the most important ELD. ELD: end-of-life decision with possible or certain life-shortening effect. More than one response was possible for each case. Percentages are row percentages. Not included in table and analyses: missing data for *involvement of professional caregivers in the decision-making process n*=76 (7.9% of all cancer deaths for which at least one ELD was made).

[a] Percentages are weighted for the disproportionate stratification and differences in the distribution of mortality characteristics between the response sample and all patient deaths.

[b] 'Other' category includes head and neck; bone and articular cartilage; skin; eye, brain and central nervous system; thyroid and endocrine glands; ill-defined, secondary and unspecified sites; independent (primary) multiple sites.

[c] Bivariate differences between patients with different cancer types calculated using Pearson's chi-square tests.

6.4 DISCUSSION

End-of-life decisions were found to be equally common in all cancer types, with particularly high euthanasia or physician-assisted suicide rates (8.7-12.6% across cancer types). Our study did not find significant differences between different cancer types regarding the prevalence of ELDs and the involvement of patients, family and professional caregivers in the decision-making process; ‘expected further suffering’ and ‘unbearable situation for relatives’ were reasons more often reported in those dying from hematological cancer than from other cancer types.

This is the first study estimating and comparing the occurrence of ELDs in different cancer types. An important strength is that it was based on a large random sample of death certificates. The population-based approach allows for international as well as national comparative research. Furthermore, the 58.3% response rate achieved is satisfactory, considering that average response rates among physicians to mailed surveys have been reported to be 54% to 61% in previous studies.[33-35] This enabled us to analyze ELDs and characteristics of the preceding decision-making process in detail by cancer diagnosis. The findings of this study need also to be considered in light of its limitations. Despite the adequate response rate, we cannot fully exclude some degree of non-response bias, nor can we exclude the possibility of social desirability bias, especially an under-reporting of ELDs that may be considered contentious. Information was gathered from the physician’s legal perspective only, thereby excluding the perspectives of patients, their families and other professional caregivers. Lastly, although physicians were encouraged to complete the questionnaire by consulting the medical file as much as possible, recall bias might have affected the results.

Our findings demonstrate that the prevalence of ELDs is equally high in all cancer types, suggesting that patients and oncologists see medical practices with a potential or certain life-shortening effect as acceptable end-of-life options. More than one in ten deaths (10.4%) were from euthanasia or physician-assisted suicide, which is a considerable increase on the 5.6% of all cancer deaths recorded in 2007[6] and substantially higher than the general rate of 4.6% recorded in 2013.[30] An important finding of our study is that this high rate of assisted dying is consistently noticeable in all cancer groups (8.7-12.6%), and that it does not differ significantly between cancer types. Taking into account that the number of euthanasia requests is higher than the number eventually carried out, this indicates that in Belgium assisted dying has clearly become a part of medical practice in the care of cancer patients and that the various disciplines of oncology need to be trained in dealing with euthanasia requests.

The administration of drugs with the explicit intention to hasten death (life-shortening acts) without the explicit request from the patient occurred in 1.8% (1.0-3.4%) of the cancer deaths during the studied period. These acts have been central in debates on physician-assisted dying as they are often seen as indicators for the development of a ‘slippery slope’- the fear that even if legislation for euthanasia sets out strict criteria and safeguards, it will lead inevitably to undesirable practices.[36,37] To date, no clear evidence has been found to support this fear. In Belgium and the Netherlands, where euthanasia has been legal for many years, the proportion of deaths in which life-ending drugs were used without explicit patient request has not risen since the legalization.[38-40] Previous studies have also identified important differences between cases of euthanasia and life-shortening acts without explicit patient request in terms of the drugs used.[41-44] An analysis of cases of life-shortening acts without explicit patient request revealed that these acts mainly involved opioids, which are seldom used in euthanasia, and which were administered in doses that were not higher than needed for pain and symptom management. The practice of using life-ending drugs without explicit patient request may thus in reality be more similar to intensified pain alleviation with a ‘double effect’ than to non-voluntary termination of life.[42,44] This, together with other studies showing that physicians tend to overestimate the life-shortening effect of opioids,[45-47] may indicate a need for education of clinicians aimed at correcting misperceptions about opioid use.

Our data revealed no difference in ELD rates in patients dying from the five most common cancers. Although symptoms and access to palliative care services have been found to differ depending on cancer type,[17,18,19] this seems not to be the case for decision-making at the end of life. A possible explanation for this may be that universal protocols, education and training of care practices across oncological settings or specialisms have resulted in a procedural, structured and uniform approach to providing care towards the end of life in cancer patients, including palliative care.

Regarding reasons for ELDs, it is not surprising that the patient’s physical suffering and the lack of prospects for improvement were mentioned most frequently by physicians, given the significant burden of symptoms that cancer patients can experience and taking into account that people with cancer have a more predictable dying trajectory compared to those with other chronic, terminal illnesses such as heart failure and chronic obstructive pulmonary disease.[13] The frequency with which the reasons ‘expected further suffering’ and ‘unbearable situation for relatives’ were reported differed by cancer type; they were most often reported in hematological cancers. The spectrum of hematological cancer is very broad, with chronic diseases and low treatment-related toxicity (e.g., chronic leukemias, low-grade myelodysplasias, chronic myeloproliferative neoplasms, indolent lymphomas) on the one hand, and rapidly evolving and lethal cancers (e.g., acute leukemias, aggressive lymphomas and multiple myelomas) on the other hand. In the latter group life expectancy is short, especially in the elderly population which happens to be the highest proportion included in this study (53.8% of patients with hematological cancer were ≥ 80 years). In this population, and taking into account the aggressive nature of these cancers as well as the poor therapeutic options, it seems logical that ELDs are more frequently inspired by avoiding further suffering and the unbearability of the situation for close relatives.

Although the majority of patients with decision-making capacity were involved in the decision-making process preceding the ELD, decision-making took place without the patient's input in almost 20% of cases. Oncologists face several barriers which may hamper effective communication with patients and families about end-of-life issues, such as personal discomfort with death and dying, diffusion of responsibility among colleagues, and lack of training in this area.[48] Nevertheless, according to the ethical principle of patient autonomy, all possibly life-shortening decisions should be discussed with the patient, unless he or she has explicitly said otherwise.[49] Also noteworthy is the low rate of written advance directives (less than 6%) and the suboptimal involvement of family members that we found in patients lacking decision-making capacity (the ELD was discussed with the family in less than 70% of cases in all cancer groups except for breast cancer). Advance care planning, which ideally includes, though is not limited to, the appointment of a proxy decision-maker and the completion of an advance directive, can be worthwhile for cancer patients when planning for the possibility of losing decision-making capacity.[50,51]

In conclusion, our results show high occurrence rates of ELDs in all cancer types. Neither the prevalence of ELDs nor the characteristics of the preceding decision-making process were found to differ greatly by cancer type, indicating that end-of-life care and palliative care are provided uniformly across cancer settings. Although our findings suggest that the decision-making process preceding an ELD is often inclusive, there is still room for improvement in encouraging the involvement of the person who is dying as well as those close to them in decision-making towards the end of life. Patients with incurable cancer and their families may benefit from the timely initiation of discussions about future treatment and end-of-life care preferences, especially those with cancers that have a higher potential of rapid deterioration, such as hematological malignancies. Therefore, embedding advance care planning into usual oncology clinical practice is crucial. Health services and policy makers need to develop strategies, guidelines, and procedures for implementation of appropriate advance care planning programs, and provide health care facilities with the necessary education and resources.

ADDITIONAL INFORMATION

Ethics approval and consent to participate

Ethical approval was obtained from the Ethical Review Board of the University Hospital of the Vrije Universiteit Brussel (ref no. 143201316288, 8 February 2013). Patients were deceased, and consent was not required. Physicians' participation was regarded as implicit consent, which was noted in the accompanying letter introducing the study.

Availability of data and material

Individual data cannot be made fully available due to data protection and privacy restrictions that were made under contract with the Flemish Agency for Care and Health, who collected the data. These restrictions prohibit the research group from sharing the collected data with others to prevent study participants from being identified. Aggregated data can be requested from the Flemish Agency (anne.kongs@wvg.vlaanderen.be) after requesting permission from the Privacy Commission (joris.ballet@ksz-bcss.fgov.be).

Conflict of interest

R.S. has reported that he has received honoraria for attendance at advisory board meetings from Celgene, Takeda, AbbVie, and Amgen. He has also received travel funding from Bristol-Myers Squibb (BMS) to attend the American Society of Hematology 2016 Annual Meeting (December 2016). All remaining authors have declared no conflicts of interest.

Funding

This study was part of the 'Flanders Study to Improve End-of-Life Care and Evaluation Tools (FLIECE) project,' a collaboration between the Vrije Universiteit Brussel, Ghent University, the Katholieke Universiteit Leuven, Belgium, and VU University Medical Centre Amsterdam, the Netherlands. The study was supported by a grant from the Flemish Government Agency for Innovation by Science and Technology (Agentschap voor Innovatie door Wetenschap en Technologie; SBO IWT no. 100036). The first author, M.V., has received funding from the 7th Framework Programme for Research and Technological Development (FP7) (proposal no. 602541-2). The funding sources had no role in the design and collection, analysis, and interpretation of data and in writing the manuscript.

Author's contributions

J.C., K.C. and L.D. contributed to the study concept and design and data acquisition. M.V., D.H. and K.C. contributed to the statistical analysis and first draft of the manuscript. All authors contributed to the interpretation of the data and further drafts of the manuscript. All authors read and approved the final version of the manuscript. K.C. and L.D. contributed equally as last author.

Acknowledgements

The authors thank the entire team of the Flemish Agency for Care and Health; Jef Deyaert, MSc, Sigrid Dierickx, MSc, and Lenzo Robijn, MSc, End-of-Life Care Research Group, Vrije Universiteit Brussel (VUB) & Ghent University; Brecht Haex, MSc, and lawyer Wim De Brock, LLM, for their contributions in the data collection. The authors thank the thousands of Flemish physicians participating in the survey. The authors thank the Belgian Medical Disciplinary Board for recommending the study and Jane Ruthven, PhD, for providing assistance with linguistic editing.

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7

General discussion

Some parts of this general discussion are based on, or to a certain degree copied from the following articles:

Verkissen MN, De Vleminck A, Groenvold M, Jabbarian LJ, Bulli F, Cools W, Van Delden JJM, Lunder U, Miccinesi G, Payne SA, Pollock K, Rietjens JAC, Deliens L. Functional impairment, symptom severity and overall quality of life in patients with advanced lung or colorectal cancer in six European countries: baseline findings from the ACTION study. *Supportive Care in Cancer,* 2021; **29**(10):5797-810. [2020 SCI impact factor 3.603; journal ranking Q1; ranking n°9 of 68 in REHABILITATION in SCIE edition]

Verkissen MN, Hjermstad MJ, Van Belle S, Kaasa S, Deliens L, Pardon K. Quality of life and symptom intensity over time in people with cancer receiving palliative care: results from the international European Palliative Care Cancer Symptom study. *PLoS ONE*, 2019; **14**(10): e0222988. [2019 SCI impact factor 2.740; journal ranking Q2; ranking n° 27 of 71 in MULTIDISCIPLINARY SCIENCES]

Verkissen MN, Penders YWH, Onwuteaka-Philipsen BD, Moreels S, Donker GA, Vega Alonso T, Van den Block, Deliens L. End-of-life communication in advanced cancer: international trends (2009-2014). *BMJ Supportive & Palliative Care*, 2020; Published online ahead of print of print, 2020 Apr 27. [2020 SCI impact factor 3.568; journal ranking Q2; ranking n° 35 of 107 in HEALTH CARE SCIENCES & SERVICES]

Verkissen MN, Leemans K, Van den Block L, Deliens L, Cohen J. Information provision as evaluated by people with cancer and bereaved relatives: a cross-sectional survey of 34 specialist palliative care teams. *Patient Education and Counseling,* 2019; **102**(4): 768-75. [2019 SCI impact factor 2.607; journal ranking Q1; ranking n° 16 of 108 in SOCIAL SCIENCES, INTERDISCIPLINARY]

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. *British Journal of Cancer*, 2018; **118**(10): 1369-76. [2018 SCI impact factor 5.416; journal ranking Q1; ranking n° 44 of 230 in ONCOLOGY]

GENERAL DISCUSSION

This part of the dissertation discusses the main findings of the five studies, aiming to explore different aspects of end-of-life care in advanced cancer patients from several countries in Europe. To realize the ***first objective*** of this dissertation (**PART I**), we described patient-reported emotional and physical functioning, symptom intensity and overall quality of life in people with advanced cancer across six European countries (**Chapter 2**), as well as evaluated patient-reported emotional and physical functioning, symptom intensity and overall quality of life and their evolution over time in patients receiving palliative care in Europe (**Chapter 3**). To realize the ***second objective*** of this dissertation (**PART II**), we described trends over time in communication about end-of-life topics with cancer patients in general practice in three European countries (**Chapter 4**), as well as explored how cancer patients who were supported by specialist care services, and bereaved relatives of people with cancer who had died while under the guidance of specialist palliative care services in Belgium evaluated information provision by these services and (in the case of the patients) their involvement in decision-making (**Chapter 5**). To realize the ***third objective*** of this dissertation (**PART III**), we examined the prevalence and characteristics of end-of-life decisions in Belgian patients with different types of cancer (**Chapter 6**).

First, a summary of the most important results of the studies undertaken to address the above-mentioned topics is given, followed by a discussion of the methodological strengths and limitations of the study designs included in this dissertation. Next, our findings are explored in depth and related to previous research and current clinical practice. Additionally, a number of challenges, implications and recommendations for future research, practice and policy are suggested.

7.1 SUMMARY OF THE MAIN FINDINGS

In the following sections, the results of the previous chapters are summarized according to the three separate parts of this dissertation.

7.1.1 PART I: Self-reported emotional and physical functioning, symptoms and quality of life in people with advanced cancer

Patient-reported emotional and physical functioning, symptom intensity and overall quality of life in people with advanced cancer across European countries

In **Chapter 2** we studied emotional functioning, physical functioning, symptom intensity and overall quality of life (QoL) as reported by a large representative sample of people with advanced lung or colorectal cancer in six European countries. We also compared these outcomes across countries. Fatigue was the most severe self-reported symptom in this sample. The second- and third-highest scoring symptoms in terms of severity overall were insomnia and dyspnea. We found some commonalities in outcomes across countries. The difference in means between the highest and lowest scoring country was smaller than 10 points (often used as a threshold for clinical relevance) for pain, nausea/vomiting and constipation; thus, the scores for these three symptoms were laying relatively close to each other. Aside from similarities, the results also revealed international differences in symptom intensity, functioning and QoL. The most remarkable overall finding was that in general, the best scores (i.e., highest for emotional functioning and QoL, lowest for symptoms) were reported by patients from the Netherlands and from Denmark, while patients from the UK reported relatively less favorable outcomes. Patients from Belgium reported worse emotional functioning than the other countries averaged.

> The results underline the essential role of healthcare professionals to consistently monitor burdensome physical and psychological symptoms when caring for patients with advanced cancer. Policy makers must take into account cross-national differences in important patient-reported outcomes and invest in providing care tailored to the needs of their population. Future research should identify which factors are most important in causing these variations between European countries.

Patient-reported emotional and physical functioning, symptom intensity and quality of life in people with advanced cancer in Europe over time

In **Chapter 3** we investigated, in a large international sample of people with advanced cancer receiving palliative care, the course of functional status, symptom intensity and overall QoL over time. We performed a prospective analysis of the entire study sample, which illustrated that emotional functioning, physical functioning, symptoms and QoL remained generally stable from inclusion (baseline) over time throughout the study duration (≥8-month follow-up). Additionally, we conducted a retrospective analysis of participants who had passed away during follow-up. This approach revealed that emotional functioning remained initially stable (when comparing those ≥6 months prior to death with those 5-3 months prior to death), but significantly decreased in the last months (when comparing those 5-3 months prior to death with those 2-0 months to death). Physical functioning, pain, fatigue, appetite loss and overall QoL showed a progressive decline towards death (those 5-3 months prior to death scored worse than those ≥6 months prior to death, and those 2-0 months prior to death scored worse than those 5-3 months prior to death). Dyspnea, insomnia and constipation only deteriorated from 5-3 to 2-0 months before death, and nausea/vomiting only showed a significant worsening when comparing those ≥6 months prior to death with those 2-0 months prior to death.

From these results, it can be concluded that deterioration of symptoms may already occur before the terminal phase, and tends to accelerate close to death ('terminal drop'). The findings accentuate the significance of early, systematic symptom assessment and management in patients with advanced cancer, and point to the need for further prospective studies to identify those factors that best predict which patients are most at risk of high symptom burden, and/or high functional and QoL impairment.

7.1.2 PART II: End-of-life communication and information provision in people with advanced cancer

Trends in communication about end-of-life topics with cancer patients in general practice in three European countries, and differences in trends in GP-patient end-of-life communication with respect to patient characteristics

Chapter 4 described a trend analysis on communication about end-of-life topics with cancer patients in general practice in Belgium, the Netherlands and Spain in 2009-2010 (Spain: 2010-2011) and 2013-2014. A representative sample of GPs registered all deceased adult cancer patients in their practice and reported for five end-of-life care topics whether they had been discussed with the patient. Overall, diagnosis was the most commonly discussed end-of-life topic in all three countries. In Belgium, significant increasing trends were found between 2009 and 2014 for communication about the diagnosis, for communication about options for end-of-life care, for GPs' awareness of patients' preferences for medical treatment at the end of life and for GPs' awareness of patients' preferences for a proxy decision-maker. In the Netherlands, significant increasing trends were found for GPs' awareness of patients' preferences for medical treatment and for GPs' awareness of patients' preferences for a proxy decision-maker. In Spain, comparable upward trends for GPs' awareness of patients' preferences for medical treatment and a proxy decision-maker were visible, but did not reach statistical significance. Besides increasing trends, we found unexpected declines over time for two topics. Both in the Netherlands and in Spain, there was a significant decrease in communication about options for end-of-life care and about psychological or social problems. In general terms, the aforementioned trends were seen across patient groups (age, gender, cancer type, place of residence in the last year of life, place of death).

These findings tell us that end-of-life communication in primary care in Europe can change considerably in a relatively short time span. Despite cross-national differences in the prevalence and magnitude of change, overall trends were similar to a substantial degree. Challenges to the continuity of communication between GPs and patients are an important point of attention. Further research should study end-of-life communication and the process advance care planning (ACP) as a whole, throughout the cancer care trajectory, and across healthcare providers of varied specialties and multiple settings.

Information provision by specialist palliative care services and involvement in decision-making: evaluations of people with cancer and bereaved relatives

Chapter 5 explored how cancer patients being supported by specialist palliative care services (PCSs) in Belgium evaluated information provision and involvement in decision-making. Furthermore, we investigated how relatives of cancer patients who had died while under the guidance of specialist PCSs evaluated information provision by these services, and how evaluations varied with respect to the patient's age and gender, length of guidance, and the type of palliative care service. Overall, the majority of patients reported positive experiences of the amount of information they received regarding their illness and end-of-life care, the extent to which their wishes were respected by professional caregivers and the opportunity to participate in decision-making about their care. Bereaved relatives' evaluations were also predominantly positive with respect to the amount of information received on the patient's illness, care and impending death. Information provision seemed to have been most satisfactory to both patients and bereaved relatives in cases where care was provided within a separate hospital-based palliative care unit (PCU) – offering personalized, continuous care – as compared to cases where care was provided by a hospital-based mobile palliative support team or a multidisciplinary mobile palliative homecare team – mainly providing support and advice to other healthcare professionals. We also found that the patient's age influenced evaluations of decision-making. Older people with cancer were more likely to have had a less active role in making decisions about their care and felt that their personal wishes were not always taken into account. Relatives of younger adult patients (18-64 years) more often reported having received less information than they considered necessary about the person's condition and treatment than relatives of older patients (65-84 years).

Our results contribute to existing literature on the benefits of PCSs by showing that these services are well equipped to delivering information and support catered to individual patient and family needs. The findings may help optimize information provision and decision-making in cancer care within the various palliative care structures, and inform other countries in the process of improving their palliative care policies. Future studies will be needed to clarify how services can learn from each other's best practices.

7.1.3 PART III: End-of-life decisions and the preceding decision-making process in people who died from cancer

Prevalence and characteristics of end-of-life decisions in different cancer types

Chapter 6 concentrated on the prevalence of end-of-life decisions with a possible or certain life-shortening effect (ELDs) and characteristics of the underlying decision-making process among people who died from different cancer types in Belgium. A nationwide death certificate study was conducted based on a large random sample of all deaths in Flanders (2013). Treating physicians completed a questionnaire concerning medical decisions made at the end of life and the decision-making process leading to the ELD. In general, the occurrence of ELDs was (equally) high in all cancer types. More than one in ten deaths (10.4%) were from euthanasia or physician-assisted suicide. This relatively high rate of assisted dying was consistently noticeable in all cancer groups (8.7-12.6%). The administration of drugs with the explicit intention to hasten death (life-shortening acts) without the explicit request of the patient occurred in 1.8% (1.0-3.4%). The two reasons most often reported by physicians for the ELD with the most explicit life-shortening intention were physical suffering and a lack of prospect of improvement. After adjustment for confounders, ELDs were shown to be more often based on anticipated further suffering and unbearability of the situation for close relatives in hematological cancers than in other types of cancer. While patients with decision-making capacity were regularly involved in the decision-making process (71.6-92.3%), decision-making still took place without the patient's input in almost 20% of cases. Remarkable was the low rate of written advance directives (less than 6%) and the suboptimal involvement of family members that we found in patients lacking decision-making capacity (ELD was discussed with the family in less than 70% of cases in all cancer groups, except for breast cancer). For those without capacity, neither the presence of a living will nor the decision being discussed with the family could be related to cancer type.

The findings may indicate that universal protocols and training of care practices across oncological settings in Belgium have resulted in a uniform approach to end-of-life care and palliative care. Irrespective of their specific diagnosis, cancer patients seem to have equal opportunities to go through the process for access to assisted dying practices, which are common within cancer care in Belgium. There is room for improvement with regard to (encouraging) the involvement of patients and relatives in decision-making. Policy makers need to develop strategies for the implementation of ACP programs and provide healthcare facilities with the necessary education and resources.

7.2 METHODOLOGICAL CONSIDERATIONS, STRENGTHS AND LIMITATIONS

Throughout this dissertation, various methodologies and study designs were used to address the study objectives and research questions. The research included is all quantitative rather than qualitative. Secondary analyses of existing data were conducted, which means that we analyzed existing data that has previously been collected for another primary purpose. While traditionally some researchers might accept the use of primary data sources as more authentic, rigorous or profound, there are several compelling reasons for using secondary data. Not only is it a time-saving and cost-efficient way of increasing knowledge,[1] it also maximizes the output of data collection efforts.[2] The latter is particularly important when undertaking research that involves people near the end of life. In such a context, patient vulnerability and the potential burden of research on participants urges extra caution.[3] Making full use of existing data to address interesting new research questions shows acknowledgement of the time and energy patients invested into filling out questionnaires. Moreover, the existence of a large amount of previously collected data provides us with a possibility to use a broad variety of techniques for analyzing data, such as international analyses, comparisons of specific subsets and research covering an extended period of time. In the following paragraphs, the key strengths and limitations of the different studies presented in this dissertation are discussed. This discussion is supposed to be understood in addition to and extending the strengths and limitations described in the discussion sections of previous chapters.

7.2.1 International cross-sectional study among people with advanced cancer (Chapter 2)

Based on baseline data from the ACTION study in six European countries

In **Chapter 2**, we reported the results of a cross-sectional survey among people with advanced lung or colorectal cancer. We used baseline patient data from the *ACTION* study, a multicenter cluster-randomized controlled trial carried out in 23 hospitals in six European countries (Belgium, Denmark, Italy, the Netherlands, Slovenia, United Kingdom) from 2015 to 2018.[4,5] A significant methodological strength of our study is that it included unique data of patients with advanced stages of the two deadliest non-gender related cancers, from countries with different healthcare systems and end-of-life cultures. In combination with the large sample size (N = 1117), this adds to the external validity of the study results.

The relevant outcome variables – functional impairment, symptoms and overall QoL – were assessed using the palliative care version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C15-PAL).[6] This measurement tool is a shorter and more focused version of the EORTC QLQ-C30 core questionnaire for measuring QoL in cancer patients.[7] The QLQ-C30 core questionnaire is one of the most extensively used patient reported outcome measures in oncology clinical practice settings.

[8,9] Patient-reported outcome data generated through patient reported outcome measures (PROMs) such as the QLQ-C30 and the QOLQ-C15-PAL are elicited directly from the patient (the 'patient experience'), without interpretation of the patient's response by a healthcare professional or anyone else. PROMs have several advantages and can be used to guide patient-centered care, which is essential for comprehensive assessment of the impact of treatment and care.[10] They may contribute to increased awareness among healthcare professionals to anticipate on individual patient needs,[11,12] promote shared decision-making[13] and assist in improving the quality of oncological supportive care.[14] The EORTC recommends the use of the EORTC QLQ-C15-PAL in patients with advanced cancer in palliative care. Since the QLQ-C15-PAL contains those QLQ-C30 items that have been identified as most important for palliative care,[6,15,16] it is also possible to compare results from different studies using the QLQ-C30 or QLQ-C15-PAL questionnaires. We took advantage of this feature in the discussion section of **Chapter 2**, where we compared our findings with those of a recent study that collected European QLQ-C30 general population norm data and individual country norms for several European countries.[17]

In order to investigate how each outcome could be explained in terms of the patients' country and considering other socio-demographic and clinical patient characteristics, we performed linear mixed-effect modeling, also referred to as multilevel or mixed modeling, as a method of data analysis. Mixed models are flexible and extend traditional linear models to allow both fixed effects (here: country) and random effects (here: hospital). Mixed-effect modeling is known as a powerful statistical technique for analyzing complex datasets, including datasets with clustered observations, as in the case of our study.[18] Interpretation of the results is restricted by the fact that this type of inter-country comparative analysis does not have a 'natural' baseline reference, and there is no set standard that decides which comparison group is most appropriate. We chose to use the category with the highest overall QoL (the Netherlands), because this choice provided the most intuitive interpretation of the results. We further addressed this issue by implementing a second data analysis method, comparing each individual country's mean score to the average mean of the other countries, for all separate outcomes. The results of this additional analysis illustrated that two parallel methods lead to roughly similar results, which strengthens the conclusions.

7.2.2 International prospective and cross-sectional study among people with advanced cancer (Chapter 3)

Based on data from the longitudinal EPCCS study in twelve countries

In **Chapter 3** we explored data derived from the multicenter *European Palliative Care Cancer Symptoms (EPCCS)* study, which was conducted in 30 palliative care centers in 12 countries (ten European countries, Australia and Canada) and ran from April 2011 through October 2013.[19] To the best of our knowledge, the EPCCS study is the most extensive longitudinal cohort study in a palliative care cancer population. Three major strengths of this study are the large geographical coverage (participants were treated at various centers in Europe and beyond), the – for palliative care – relatively long duration of follow-up and the large sample size (1739 patients with incurable cancer enrolled in a palliative care program).

The palliative care version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C15-PAL)[6] was used to measure functioning, symptoms and overall QoL. As we have previously mentioned, this questionnaire has shown to be valid for QoL evaluation in our target population (advanced cancer patients in palliative care).[6] A unique aspect of our study is that we reported the results of two different data analysis methods. The first method was a broad, prospective analysis of the entire study sample, from study entry to ≥8-month follow-up. This method, however, did not lend itself for thorough conclusions on the stability or worsening of these outcomes *towards the end of life*, because patients who were still alive at the end of the follow-up period were also included in the analysis. We conducted a second method, a retrospective analysis including only those patients who had died during follow-up. This method allowed us to compare the results of three cross-sectional subsamples based on time prior to death (≥6, 5-3 and 2-0 months). The retrospective cross-sectional findings yield a more concrete picture of functional impairment, symptoms and overall QoL at different stages of the incurable/terminal disease. Linear mixed-effects (multilevel) models were estimated to analyze the data. Many commonly used statistical techniques assume independence of the observations or measurements and should not be used in this situation, because ignoring the correlation between repeated measurements can lead to biased and invalid results. Proper repeated-measure data analysis requires the implementation of more innovative methodologies. Linear mixed modeling is one of the best-known techniques for the analysis of longitudinal and/or hierarchical data.[20] By using these types of models, we accounted for the repeated nature of the data and the fact that observations on subjects who share common characteristics (patients treated in the same hospital and hospitals located in the same country) are likely more similar to each other than to observations of subjects from another cluster.

The study has some significant caveats. In longitudinal studies, particularly in palliative care populations, attrition/drop out as a consequence of symptom deterioration or death remains a fundamental problem. Data scarcity is clearly visible in the last months of the study. A further issue arising from this study concerns the study's external validity and the representativity of the patient sample. Centers were selected through non-random recruitment based on self-selection, and participating institutions were predominantly hospitals that offered anti-cancer therapy as part of their palliative care programs. In addition, sampling procedures were not identical: some centers performed consecutive sampling (i.e., every subject meeting the criteria of inclusion is selected until the required sample is achieved), whereas others recruited a convenience sample due to staffing shortages. While we cannot rule out the risk that the frailest patients were not included in this study, we expect that the impact of sampling bias on the results has been rather limited, given the sample size of more than 1600 patients, and in comparison to other studies among palliative care and advanced cancer patients.[21]

7.2.3 Mortality follow-back study among general practitioners (GPs) of cancer patients in representative epidemiological surveillance networks (Chapter 4)

Based on the EURO SENTIMELC study in Belgium, the Netherlands and Spain

In **Chapter 4**, we presented data that were collected in Belgium, the Netherlands and Spain (Castile and León) as part of the *European Sentinel Network Monitoring End-of-Life Care (EURO SENTIMELC)* study in 2009-2010 (Spain: 2010-2011) and 2013-2014. The EURO SENTIMELC study is an ongoing mortality follow-back study designed to retrospectively monitor end-of-life care in population-based samples of deaths in different countries.[22] Data were gathered from existing nationwide epidemiological surveillance networks of general practitioners (GP Sentinel Networks) in the countries that were studied. These networks consist of GP practices or community-based physicians who constantly monitor one or several indicators of health problems among their patients – information that can be used to keep a continuous record of the health of the full population. In Belgium, the GPs were selected to form a representative sample of GPs, covering the whole country. Every year, the responsible Institute for Public Health kept track of the network's stability and verified its representativity comparing age, gender and geographical distribution of the sentinel GPs with characteristics of the total GP population in Belgium. In the Netherlands, GPs were also selected to cover the country as a whole. Age, sex and geographical distribution and urbanization were compared with the total GP population on a yearly basis by the responsible institute to confirm the representativity of the GP sample. Furthermore, the sample of the population reached by the sentinel GPs was yearly compared with the entire patient population in terms of age and gender to verify the network's representativity (this was not possible for Belgium, because patient lists were lacking). In the case of Spain, similar procedures as in the Netherlands were performed within the autonomous community included in the study (Castile and León) to ensure representativity at GP and patient level.[22] GPs from the networks regularly completed a questionnaire about all patients of their practice who died recently. Non-sudden cancer deaths were included in our study (total $N = 2306$).

The use of a retrospective population-based research method has advantages and disadvantages.[23] The greatest strength of this method is that it provides estimations of the prevalence of end-of-life care practices – such as end-of-life communication – in a population as a whole.[24] Prospective research with the aim of studying end-of-life care is often not feasible in practice, as it can only base itself on setting (e.g. include those individuals who enter a certain program or hospital ward), diagnosis or (likely unreliable) prognosis.[23,25,26] In addition, those who were diagnosed very late in the disease trajectory are usually not included. Retrospective surveys are by definition not hampered by lost to follow-up, and are mostly time- and cost-efficient. One of their biggest weaknesses is that they use proxy respondents – GP, the next of kin – and not the patient.[23] In general, proxy reports have been shown to be reliable (i.e., congruent with the patient's own judgement) with regard to observable symptoms, care received and the quality of services, and less reliable with regard to more subjective elements of a patient's experience, such as emotional discomfort and pain.[27] It is important to remember that causal inferences cannot be made with retrospective research, even though some explanations are naturally more plausible than others. Another downside of these types of studies is that they are vulnerable to recall bias. People may remember emotionally loaded experiences (negative as well as positive) more easily than neutral experiences.[28] There are certain strategies that may reduce recall bias; in our study, for example, GPs were instructed to complete a questionnaire within a week of the patient's dead.

The representativity of the GP Sentinel Networks means our findings are transferable to the general population. Because the networks have been collecting data for some years, we were able to perform trend analyses to see how end-of-life communication practices in primary care in Europe for people with advanced cancer have evolved over time. One caveat of this specific design is that the data provide only the GP's viewpoint.[23] No information was available on communication about end-of-life topics with informal or formal caregivers other than the GP. We must also keep in mind that perceptions of what constitutes the 'discussion' of a certain topic may differ between patients and physicians.[29] The data covers only the prevalence of discussions and can neither provide in-depth insights into patients' expectations/preferences for such conversations nor into the quality of the communication process. It is not known, for instance, whether communication about care preferences was started early enough to make a material difference to the quality of end-of-life care. However – it was not within the scope of this study to provide a full picture of the totality of practices regarding communication at the end of life between healthcare providers and cancer. In spite of that, the current work is still interesting for its unique focus on similarities and/or differences in trends (i.e., the prevalence and magnitude of change over time) in communication around end-of-life care in primary care for people with advanced cancer across three European countries and diverse patient groups. A last constraint is that – although representative within this area – the Spanish Sentinel Networks only covered a certain area (Castile and León) leading to a smaller sample and lower statistical power. This could possibly have led to an underestimation of the significance of some results.

7.2.4 Nationwide retrospective cross-sectional study (Chapter 5)

Based on the QPAC study in Flanders, Belgium

Chapter 5 had the aim to investigate information provision, including information about end-of-life care by different types of different types of palliative care services from the perspective of both people with advanced cancer and their relatives. This national cross-sectional survey was part of the more comprehensive *Quality Indicators for Palliative Care (QPAC)* study in Flanders, Belgium.[30-32] Questionnaires were administered at one moment in time during four measurement periods (in 2014, 2015 and 2016) within 34 specialist palliative care services (PCSs). A snapshot approach was followed: the cross-sectional inclusion method used during every measurement period required the palliative care teams to make a random selection of two groups of patients on one given day (the day of assessment) with a maximum of 50 in each group, people who were under the guidance of PCSs on that specific day and people who had died under the guidance of PCSs between the previous four weeks and four months.[30] For the first group, questionnaires were sent to the patient with cancer (or a representative), for the second group, questionnaires were sent to the most significant relatives, mostly partners. A questionnaire was received from N = 628 cancer patients who were supported at the time of the measurement, and from N = 980 relatives of deceased patients.

This study adds to the growing literature on the benefits of PCSs by showing differences between types of PCSs (multidisciplinary mobile palliative homecare teams, hospital-based palliative care units (PCUs), hospital-based mobile palliative support teams) regarding information provision about the illness and end-of-life care as evaluated by patients and bereaved relatives. A few limitations must be considered. The survey only asked respondents whether they had received 'the right amount of' information about the described topics. We do not know whether they were satisfied with the content, detail and timing of the information. It remains also unknown how much information actually was provided. Furthermore, changes in disease status can influence the patient's preferences for information and involvement of decision-making; however, the design of this study did not allow for studying changes over time along the illness trajectory. A final shortcoming of the present study is that different items were used for the two populations of interest, making it impossible to compare patient responses with those from relatives.

7.2.5 Nationwide retrospective death certificate study (Chapter 6)

Based on the ELD study in Flanders, Belgium

Chapter 6 studied the prevalence of end-of-life decisions with a possible or certain life-shortening effect (ELDs), characteristics of ELDs and characteristics of the preceding decision-making process among people who died from different cancer types in Flanders, Belgium. We looked at results from a nationwide death certificate study conducted based on a large, representative random sample of all deaths in Flanders, Belgium (January-June 2013), stratified of the likelihood of an ELD being made. A questionnaire asking about medical decisions made at the end of life and about aspects of the decision-making process was completed by attending physicians (N = 1394).[33] A strong advantage of the *ELD* study is that by using death certificates, we were able to collect robust data for the entire population. This is known as a highly reliable method for describing end-of-life care.[34-37] The retrospective nature of this study is also not impeded by problems of patient burden or non-response of the people who are most frail, problems that are frequently found in prospective study designs.[38] Another strength of the ELD study is related to the fact that the use of death certificates reduces bias introduced by the selection of physicians, as opposed to other types of end-of-life research where physicians are selected based on their interests in, or attitudes towards ELD practices. Moreover, unlike a prospective design, a retrospective (post-mortem) design does not imply any danger that the study will directly influence physicians and end-of-life practices.[37]

One of the major disadvantages is that it is impossible to completely exclude some degree of non-response bias, i.e., the type of bias that occurs when people are unwilling or unable to respond to a survey because of a reason that makes them differ substantially from people who respond. Similarly, we cannot rule out the possibility of social desirability bias, particularly an under-reporting of ELDs that may be considered contentious. Information was only provided from the GPs' legal perspectives. This design excludes the equally important perspectives of patients, their families and their professional caregivers[33] (in Belgium, death certificates do not allow for the identification of next of kin either way). Another limitation is that in some cases, the physician signing the death certificate was not in a position to complete the questionnaire because he/she was not the treating physician for the patient in question. On such occasions certifying physicians were given the instruction to transmit the questionnaire to the treating physician; however, sometimes the treating physician's identity turned out to be unknown. These cases were considered impossible to study and hence discarded. Lastly, and as mentioned earlier, recall bias is always a risk in retrospective research. Added to this is the fact that death certificates need to be reported to – and processed by – the proper government 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. The possibility that this delay may have affected recall cannot be excluded. In order to minimize the likelihood of recall bias, physicians were encouraged to consult the medical files (mostly readily available for them) as much as possible when completing the questionnaire.[37]

7.3 DISCUSSION OF THE MAIN FINDINGS

In the sections below, the major findings of the studies presented in this dissertation are discussed in light of current challenges and the state of affairs within palliative care research and clinical practice. The nature of the study designs and methodologies discussed above in this chapter should be kept in mind when interpreting the results.

7.3.1 PART I: Self-reported emotional and physical functioning, symptoms and quality of life in people with advanced cancer

The symptom experience of patients with advanced cancer

Many patients with advanced illness suffer from incapacitating symptoms and impairments in daily functioning or QoL. Therefore, knowledge of symptoms is a critical part of follow-up care during curative as well as life-prolonging cancer treatment. Among the two large advanced cancer samples studied in **Chapter 2** and **Chapter 3**, fatigue was overall the worst scoring (most severe) self-reported symptom. This finding corresponds to previous reports on symptoms in patients with advanced cancer,[39-45] which accentuates the significance of this problem in this population. It is important to note that fatigue felt by advanced cancer patients generally differs from the 'normal' fatigue of daily life.[46] It has been defined as a 'distressing, persistent, subjective feeling of physical, emotional and/or cognitive tiredness associated with cancer or cancer treatment.'[47] Qualitative research has confirmed that the experience of cancer-related fatigue varies greatly across patients. How it manifests itself and interferes with life is highly personal to each individual.[48] Besides fatigue, multiple other debilitating symptoms place a substantial burden on patients with advanced cancer. In terms of self-reported severity, important symptoms emerging from the above-mentioned chapters combined included dyspnea, pain, insomnia and appetite loss, where nausea/vomiting, in contrast, seems to have been relatively well controlled in both samples, with lower levels of severity overall.

Previous work has indicated that cancer patients experience symptoms throughout their illness trajectory towards the end of life, and that the burden is likely to increase as the disease progresses.[49-52] Our findings (**Chapter 3**) confirmed this by showing that some symptoms – dyspnea, insomnia and constipation – as well as outcomes such as emotional functioning seem to remain fairly stable until they deteriorate relatively shortly before death, whether other symptoms – pain, fatigue and appetite loss – and outcomes such as physical functioning and overall QoL tend to start declining 'as early as' months before the final phase of life, and deteriorate more rapidly when the time of death comes closer. This is why quality care requires systematic symptom assessment and management throughout the illness trajectory, not only at the end of life but also earlier in the course of the progressive disease. For example, this could include the routine use of questionnaires which center the patient experience, known as patient-reported outcome measures (PROMs), for systematic detection of problems and needs.[53] Unfortunately, referrals to palliative care are often not initiated until late in the course of the illness,[54-59] even though the majority of oncologists value early palliative care referral[56,60] and believe that earlier engagement with palliative care specialists improves symptom management, health-related communication and continuity of care.[43,55,56] Literature indicates that one important reason for the underutilization of early palliative care is the negative connotation attached to the label ‘palliative care’. There is widespread misunderstanding among patients, healthcare providers and the general public that palliative care is synonymous with end-of-life care, when in fact, it includes a far broader range of services.[59,61] In response, some specialists have called for a *rebranding* of palliative care to highlight its benefits for people in many different situations, reduce the stigma and make the term more acceptable to all involved.[58,62,63] At any rate, efforts to increase early palliative intervention in advanced cancer patients are strongly needed. To be able to deliver appropriate patient-centered care based on problems and needs assessment, it is vital for healthcare providers to pay attention to symptoms and other patient-reported outcomes during the *entire* illness and care process.

Different challenges for different countries in Europe: variations in healthcare organization

Our study described in **Chapter 2** revealed similarities as well as significant dissimilarities between six European countries in patient-reported functional status, symptoms and QoL. It is not easy to find out what exactly causes the variations in patient outcomes that exist between European countries, as the explanation is likely to include a wide range of factors that may be in play but are not yet fully understood. It is beyond the scope of a single dissertation to give an exhaustive description of all (interactions of) potentially relevant factors; however, a few possibilities for explaining cross-national differences in the aforementioned patient outcomes can be suggested.

Disparities between countries in patient outcomes may arise from the fact that health and social cancer care services are organized in different ways in different European countries.[64] National cancer plans have been adopted in many European countries in the course of the last decade,[65] but each system has its own context and environment. Various current cancer care practice patterns may have evolved under the influence of historical aspects, population characteristics (e.g., size, density, geographical distribution), healthcare structures, resources available within the health care system, or past and present government policies.[66] As long as a system performs well, is cost-effective and yields desirable outcomes, there is no reason to change its basic structure. And if different approaches intend to serve the same purpose, it is not necessary to impose identical manners everywhere. In many systems, however, there might be room for amendment or improvement. The performance of healthcare services in different countries can be evaluated using a number of indicators. One example of such a performance indicator is the *availability* of different services (e.g., availability of trained palliative care staff; appointment waiting list time; the number of services a patient can choose from).[67-69] Another example is the *access* to healthcare services (e.g., geographical accessibility; affordability; restrictions due to social and cultural barriers; restrictions or delays – longer waiting times – due to internal procedures or bottlenecks in the healthcare system).[70] A final, important performance indicator is the *quality* aspect of cancer care, which can be subdivided in three domains: quality of *structure* (material and human sources needed, organizational factors, access to medical technologies, availability of multidisciplinary teams), *process* quality (sum of actions that make up health care, shaped by clinical and policy guidelines, monitored through cancer registries and partly reflected by patient satisfaction) and quality of *outcome* (can be measured by health-related QoL).[70]

To summarize, it might be that higher or lower performances of different countries' health services can be partly explained by inequalities in availability, accessibility or quality of services. National policy makers acknowledge that reliable performance measurement is essential for multiple different stakeholders within a country's healthcare system to be able to facilitate high-quality services.[71] In this context, there has been increasing interest in the use of standardized outcome assessment methods[72] and the measurement of patient-reported outcomes.[73] More steps have also been taken to study and benchmark quality of care across countries, for example by the EU Commission[74] and the Organisation for Economic Cooperation and Development (EOCD).[75]

Different challenges for different countries in Europe: variations in culture

The observed differences between the six countries studied in **Chapter 2** – Belgium, Denmark, Italy, the Netherlands, Slovenia and the UK – in patient-reported functional status, symptoms and QoL might also be (partly) explained by the fact that these countries represent a multiplicity of cultures, ethical, religious and political backgrounds.[76] Europe is a continent that is characterized by cultural diversity. Culture refers to a large set of mostly intangible aspects of daily life, including language, knowledge, skills of people, and how these are influenced by religion, ethnicity, socio-economic status, and the way people look at legislation and ethics.[77] Variations in norms, attitudes and other cultural aspects influence many aspects of life, including our health. It is known, for instance, that life style factors such as health-related behaviors can make a significant difference with respect to people's health and their physical, psychological and social wellbeing.[78,79] Health outcomes are also likely to be affected by 'collective health behavior' in the shape of national health care policies.[76] The concept of culture is fundamentally relevant to health care at all levels. It affects the way people with cancer perceive their illness and/or its treatment and may play a considerable role in communication, interactions with healthcare providers and medical decision-making processes.

In our study, the Netherlands and Denmark came across as the ‘best performers’ of all six countries included in our study (highest emotional functioning and QoL scores, lowest symptom scores). While being distinct nations with unique characteristics, the two countries show similarities on several levels. Both countries have state-sponsored, well-functioning healthcare systems with good accessibility.[80,81] The Netherlands and Denmark both have a Protestant Christian heritage, although in both nations only a small part of the population actively practices their religion.[82] Protestant cultures are generally more progressive and less opposed to euthanasia than Catholic cultures (dominant in countries with a long Catholic tradition, such as Belgium and Italy),[83] suggesting potentially a more liberal approach to end-of-life care decisions such as intensifying alleviation of pain and symptoms, even if it may hasten death. The 2020 edition of a landmark survey of the state of global happiness, the ‘World Happiness Report’,[84] shows that of all 153 countries included, the Netherlands has been ranked the sixth happiest country in the world, where Denmark takes the second place – and has consistently ranked among the top three world’s happiest countries in previous years. (NB: Belgium, Italy, Slovenia and the UK occupy position 20, 30, 37 and 13, respectively.)[84] The high scores in this study could possibly be a natural consequence of the high baseline happiness in these countries.

In the UK, the results were generally less favorable. Compared to the Netherlands, the highest scoring nation overall, the UK had significantly lower average physical functioning and higher constipation. Compared to all other countries averaged, the UK reported significantly worse fatigue and dyspnea. However, it should be noted that this may in part be due to the influence of the low dyspnea score in Slovenia on the average mean. The low dyspnea score in Slovenia is explained by the fact that one of their participating centers was an institution specialized in lung diseases (University Clinic of Respiratory and Allergic Diseases, Golnik). Furthermore, as described in the discussion section of **Chapter 2**, different types of disparities in the UK, e.g., socio-economic inequality and inequalities of access to quality health care may have contributed to the outcomes. The data were gathered in areas that are relatively poor (North West and East Midlands) compared to the South, and deprivation might be a feature of these areas. Lower levels of health literacy in these areas could also have played a part, because this is associated with delayed cancer diagnosis and treatment.[85] Furthermore, for more than a decade, the National Health Service (NHS) has been chronically and badly underfunded, and health expenditure on cancer care is below average relative to other countries.[86,87]

It is most likely that the inter-country variation in our study is caused by a combination of differences in the performance of healthcare services on the one hand and differences in cultural aspects on the other. Within the context of our study, we have not been able to explain which part could have been related to differences in healthcare organization and which part could have been related to culture.

7.3.2 PART II: End-of-life communication and information provision in people with advanced cancer

Discussing diagnosis, options for end-of-life care and psychological or social problems in primary care

A vital subject in the care of advanced cancer patients is communication and information provision. In **Chapter 4**, we presented the results of a trend analysis on end-of-life communication practices in primary care in Europe for people with advanced cancer. We looked at the frequency of people with cancer with whom certain end-of-life care topics were discussed according to GPs in Belgium, the Netherlands and Spain. The prevalence of end-of-life communication between GPs and people with cancer depended on the topic discussed. In all three countries, diagnosis was found to be the most often discussed end-of-life care topic (84%-96% in 2014), while discussing other topics seems to have been less popular or more challenging.

The physician-patient relationship has gone through a major transition in the past decades, from the traditional paternalism-based model – which assumes that the doctor decides what is in the best interest of the patient, who is a passive receiver of care – to a patient-centered approach that emphasizes the development of mutually beneficial partnerships between patients and healthcare providers.[88,89] A core element of this approach is shared decision-making, and effective shared decision-making requires that patients are appropriately informed about their medical condition. Until the later decades of the 20th century, medicine was dominated by paternalistic attitudes, and this was also expressed in general ideas on the subject of truth-telling in health care. Physicians often would not disclose a terminal cancer diagnosis to a patient, for example to prevent the person from psychological distress.[90] However, healthcare providers have a tendency to underestimate patients' information needs[91] and overestimate their illness knowledge and understanding.[92] Although in some cases patients prefer not to have full information about their health condition or serious diagnosis, the vast majority of patients, including cancer patients,[93-96] want to receive detailed information about their disease and expected outcomes. Perspectives have changed and these days, with respect for autonomy as a fundamental principle in end-of-life ethics,[97] patients have the right to be told essential information that their doctors have about them and their diagnosis. Adequate information provision reduces uncertainty, builds on trust, assists patients in making informed decisions about their care and treatment, and helps them plan ahead for the future.[98] Withholding medical information can even be harmful because patients who are not be told the truth about their situation may be unable to get the needed medical support.[98]

Whereas the issue of truth-telling is still handled differently in different countries and cultures,[99] and healthcare providers often remain reluctant to disclose and discuss information concerning the (advanced illness) diagnosis,[100] there has been a growing global trend toward disclosing the truth. Most Western countries today have implemented a legal requirement for doctors to properly and honestly inform patients with regard to their condition.[99] This general trend to tell patients about a serious diagnosis seems to be reflected in the high percentages of communication about diagnosis we found across countries in the current study. The rise in communication about this topic between 2009 and 2014 (only statistically significant in Belgium; but in the Netherlands a ceiling effect might have been present, as the prevalence was already 96% in 2009) could have been a result of certain nationwide initiatives in this area. Since 2000, efforts were for example made in these countries to expand opportunities for palliative care training and the implementation of programs and guidelines to enhance end-of-life communication practices.[101-103] In Belgium, nationwide initiatives included increased reimbursement to allow GPs more time for consultations to announce the diagnosis, the realization of extra communication training courses for physicians, and the availability of protocols for delivering bad news, like a (terminal) cancer diagnosis, to patients.[102,103] Spain, in contrast, continued to develop palliative care and to integrate it in educational programs,[101] but did not pay such close and particular attention to communication. We should, however, be cautious not to overreach in drawing conclusions from this information, because the item in question ('Was the topic of diagnosis addressed during your conversations with the patient?') is broad and therefore limited in nature. It is not clear from our data whether conversations about the diagnosis might or might not have included communication and information about, for example, prognosis.

Do GPs know and address what their patients want?

GPs' position at the heart of the healthcare system and their potential to establish long-term, ongoing relationships with their patients places them in a good position to initiate communication about end-of-life care and to encourage patients and families to talk about their personal needs, values and preferences. Advance care planning (ACP) is widely promoted as an important part of end-of-life policies by policy makers in high-income countries.[104] The potential benefits of timely initiating a dialogue about ACP are well known. ACP is an ongoing process in which patients' options and preferences for treatment and care are expressed, determined, reconsidered if needed and, if they wish, documented.[105] It involves conversations about goals of care and preferences for treatment between patients, their relatives and healthcare professionals. The process can result in one or more outcomes. These might include the setting out of general views and values related to care and treatment, the completion of a document (advance directive, or 'living will') specifying the patient's preferences in various (future) situations.[106] The patient may also choose to designate a substitute decision-maker in anticipation of a time when he/she does no longer have adequate decisional capacity.[107] ACP improves communication between patients, families and physicians, helps them prepare for current as well as future healthcare decisions (including planning for the end of life), facilitates access to palliative care services, and leads to better patient satisfaction and bereavement adjustment among relatives.[107,108]

According to our results, there appears to be an overall trend over time among GPs to becoming better informed about cancer patients' preferences for medical treatment at the end of life as well as about their preferences for a proxy decision-maker at the end of life (**Chapter 4**). Increases in these two items were visible in all three studied countries between 2009 and 2014. In Belgium and in the Netherlands, the trends were statistically significant. Spain showed similar upward trends but these did not achieve statistical significance, which is likely due to poor statistical power levels in this country. These findings look promising. They seem to reflect GPs' increasing awareness and perhaps recognition of these specific aspects of advance care planning (ACP). If the GP is aware of a patient's choice of a surrogate decision-maker, it will be easier for them to reach the assigned relative within a short timeframe (preferably via a direct line) to discuss the treatment and care process. Unfortunately, the study conducted did not collect any information on the actual behavior of GPs in relation to their contact with patients – so if it is genuinely true that GPs are increasingly gaining greater awareness of their patients' preferences for treatment and proxy decision-maker at the end of life, it remains unknown so far whether, and how they act upon this knowledge.

Next, one could argue that the observed upwards trends are just following general patterns of enhanced interest in relatively recent concepts such as ACP and patient-centered communication in Europe. Both have been receiving greater policy attention over the past years, and in several countries attempts have been made to realize and implement palliative care education, training and protocols. The increasing courses of GPs' awareness of preferences for medical treatment and for a proxy decision-maker at the end of life are encouraging to see, but must be interpreted with some caution. The two 'ACP-related' items included in our analysis are indirect rather than direct indicators of ACP, and are both very specific, representing only a fraction of the total and dynamic ACP process. Therefore, we cannot make any statements about the entire process.

The importance of effective communication and information sharing between professionals at the primary and secondary healthcare level

In the discussion section of **Chapter 4**, we argued that part of the explanation for the decreasing trends in communication about options for end-of-life care and psychological or social problems could lie in the phenomenon of increasing specialization and task differentiation in primary and secondary care. Literature has shown that cancer patients may 'disappear' from the GP's practice into hospitals, where they spend more time under specialist care during and after treatment.[109-111] In the case of our study, conversations about options for end-of-life care and about psychological or social problems may have happened increasingly more often with, for instance, specialist cancer nurses in hospitals. Nurses and specialist nurses are playing a growing role in healthcare systems all over Europe.[112-114] Compared with other healthcare professions, they spend a relatively great deal of their time in the proximity of cancer patients, which helps build trust and understanding.[115] Prior research has shown that some cancer patients even prefer clinical nurse specialists (with whom they may have close relationships, and who devote particular attention to responding to their emotional needs across the care continuum) over GPs as their main source of support, and this seems particularly true for psychological support.[116]

Qualitative research on the position of GPs in continuous primary end-of-life care shows that people who are terminally ill often assign GPs a prominent role in diverse aspects of two forms of continuity. 'Relational continuity' refers to maintaining a continuing relationship with the same GP. Examples are keeping in touch after referral and feeling responsibility towards the patient. 'Informational continuity' refers to utilizing information about the patient, such as the patient history or individual circumstances to deliver tailored, personalized care. Examples are proper exchange of information across GPs, specialists and healthcare facilities. Barriers identified by patients were for instance too little time and a lack of the GPs initiative.[117] A qualitative study conducted in the Netherlands[118] reported that patients did not just place importance on the role of the GP in itself, but also on decent collaboration and transparency between healthcare professionals. When only the GP and one other partner were involved, in this study usually community nursing staff, patients and relatives generally experience this collaboration as positive. However, if multiple disciplines from primary and secondary care were involved in a patient's care, particularly specialist physicians, it could lead to errors and miscommunication, necessitating a more active role from patients and relatives themselves. Some patients also reported a lack of coordination, and hence ambiguity about one's central contact, which caused them significant distress. They felt they were being sent back and forth between the primary and secondary care providers in some situations where numerous disciplines were involved due to metastases or comorbidities.[118] These findings highlight the need for frequent communication between GPs and other healthcare providers, even in cases where one particular role (such as the GP) is seen by the patient as the main point of contact and care.

Experiences of Belgian cancer patients and relatives regarding information provision and their involvement in decision-making in specialist palliative care services

Our findings indicated that a great majority of people with cancer being supported by specialist palliative care services (PCSs) and bereaved relatives of cancer patients who had died while under the care of PCSs appeared to be generally satisfied with information provision, indicating that they had received 'just the right amount' of information about the illness and (end-of-life) care (**Chapter 5**). Patients' involvement in decision-making was also generally positively evaluated. Over half of the cancer patients reported that they were always given the option to participate in decision-making about their care, and that all of their professional caregivers took account of their personal wishes. Previous work has suggested that information provision is a commonly reported unmet need among cancer patients[119] and that information about palliative or end-of-life care is often not provided, not even in cases where patients had late-stage illness.[120] In Belgium, the patient's right to be informed – but also the right not to be informed on his/her explicit request – is one of the main principles prescribed by the Act on Patients' Rights which took effect on 22 August 2002.[121] Our research suggests that patients with advanced cancer and relatives are more likely to have their information needs met in an environment of specialist palliative care. This study thus adds to the growing literature on the benefits of specialist palliative care services. These services are well designed to be engaged with patients and responsive to individual and family needs and preferences because of their focus on delivering personalized care.[122,123]

Nevertheless, we found substantial differences between different types of PCSs. The type of PCSs turned out to be significantly associated with perceptions on information provision. Information provision seemed to have been more satisfactory to both the patients and the bereaved in the case of separate hospital-based palliative care units (PCUs) than in the case of mobile palliative support teams offering support and advice to regular healthcare professionals in the different hospital wards. These findings correspond with the results of similar work by Vermorgen et al. (2018) demonstrating that family caregivers of patients who died in a PCU reported to have received more information, support and aftercare than those of persons dying when they were being supported by a palliative support team in a hospital or a mobile homecare team.[124] The structure of hospital-based PCUs appears most effective in facilitating a supportive environment for optimal information provision, probably because the patient and/or family members are addressed in a more *tailored* and *direct* way.

Shared decision-making in cancer care: are older people being heard?

Chapter 5 showed that patients' age was significantly related to evaluations of decision-making. More specifically, older patients (65-84 years) were more likely than younger adult patients (18-64 years) to indicate that they had never or only sometimes been given the opportunity to co-decide about their care. Furthermore, compared with patients aged 65-84 years, patients aged 85 years and older (the 'oldest-old') were more likely to have had none or only some of their caregivers take their personal wishes into account. This leads us to the question whether these results are possible indications of ageism in decision-making near the end of life. From literature, it is known that ageism – stereotyping, prejudice and discrimination against people on the grounds of their age – is a global concern, highly common across countries,[125,126] that will likely increase even more with population ageing. It may be reflected in clinical practice and decision-making processes, and can significantly impact people's health and wellbeing.[127]

In general, older patients are less likely to be actively involved in medical decision-making than younger patients.[127] Physicians' assumption that older cancer patients desire less information and wish to leave decisions to their healthcare providers has been shown to be an important barrier to older patients' participation in shared decision-making.[128] This could lead to inequity in the quantity and quality of care provided to older patients and, consequently, in their health outcomes.[127] Qualitative research among healthcare providers also showed that providers are inclined to address the younger relatives of older patients, thereby bypassing the patient. Explanations mentioned were for example that they are unaware of discriminatory tendencies in their communication routines, or just presume that younger family members are faster when it comes to hearing and understanding information.[129]

Evidence tells us that people who actively participate in decision-making are usually more informed, better able to assess risks and benefits, and less likely to experience decisional conflict and dissatisfaction.[130-135] Active participation has also been associated with positive health outcomes such as better overall QoL and higher physical and social functioning.[96,136] Therefore, healthcare providers are strongly encouraged to empower older individuals to be involved in the decision-making process.[137-139] However, although the majority of cancer patients want to be involved in medical decisions,[135,137,140,141] patients vary considerably in their preferred degree of involvement.[136] In foregoing studies, it has been shown in several populations, including people with cancer,[96,142,143] that older patients tend to prefer a less active role in medical decision-making, whereas younger patients generally prefer greater involvement or a shared role.[136,140,142,144-149] 'Pushing' patients to be an active participant in medical decision-making if they do not want to be in this position is a bad idea, since it can have adverse consequences such as decisional regret,[150] increased anxiety,[151] a lack of confidence in decision-making and stress.[145] On the other hand, a lower participation preference should not automatically and immediately be equated with an *actual* wish to be uninvolved in decision-making, because such a preference might also arise from a fear of not being competent enough to make a sensible contribution to the discussion and/or slowing down the conversation.[149] This may be particularly relevant in cases where patients have limited health literacy, which is more common among the elderly.[152,153] Physicians will need to spend more time communicating with older cancer patients, and should probe and ask them more directly about their wishes. Doing so helps creating a clearer understanding of their choices and preferred level of involvement in decision-making, and enables them to respect and respond to their unique goals, values and preferences – the cornerstone of patient-centered care.[154]

7.3.3 PART III: End-of-life decisions and the preceding decision-making process to people who died from cancer

Suboptimal involvement of cancer patients and families in decision-making towards the end of life in Belgium

If the illness is terminal, the experience of anticipating death is often overwhelming to those who are dying and those who are grieving a loved one's impending passing.[155] All those involved may find themselves confronted with a number of complex, sensitive decisions that should be made regarding treatment and care near the end of life.[156,157] The results described in **Chapter 6** shed light on the extent to which patients dying with cancer in 2013 in Flanders, Belgium, and their families were involved in the decision-making process preceding an end-of-life decision (ELD). ELDs, as a reminder, are medical practices that have the potential to hasten the patient's death, either implicitly (when death is an anticipated, yet unintended consequence of the medical decision), or – less commonly – explicitly (when death is the intended outcome of the decision).[34,158] Our findings revealed that in approximately 20% of cases where the patient was judged competent at the time, he/she was nevertheless not involved in the decision-making process preceding the ELD. Although this is a better result than that of a previous study by Pardon et al. (2012) among advanced lung cancer patients where 50% of the patients, according to their physicians, were barely or not at all involved in end-of-life decision-making,[159] it still seems suboptimal. Patient engagement in healthcare decision-making is considered central to patient-centered care and is specifically important towards the end of life, because end-of-life decisions are strongly sensitive to personal values and preferences.[160-163] Involving patients in discussions regarding end-of-life care has several possible benefits such as an improved dying experience for the patient, and lower levels of psychological distress among family members.[156,164] Studies also have repeatedly illustrated that most cancer patients prefer to be involved in medical decisions.[135,165] However, several barriers to patients' active engagement in ELDs exist. Recurrent themes/barriers to initiating end-of-life conversations from the perspective of physicians across studies were for example related to time constraints and a lack of training, difficulty in making prognoses, cultural differences and perceived hesitation of the patient or family.[166]

One possible explanation for the substantial number of patients in our study who did not have input in decision-making despite having decisional capacity, may lie in the fact that conversations about the end of life are still often seen as demanding and stressful,[167] even though there is consistent evidence that conversations about individual goals and values foster preference-aligned care for patients with serious illness and improve end-of-life communication and decision-making.[168] Physicians may feel uncomfortable talking with patients about the stigmatized subject of death or dying, finding it hurtful for both the patient as the clinician. Furthermore, they may focus too much on cure and inappropriate treatment, have concerns about ethical or legal issues, lack experience with conversations about end-of-life issues, or the tools, guidelines, education and training around end-of-life communication available to them may be inadequate.[156,169] Another possibility might be that certain ELDs have become such common practice in cancer care, that physicians may not always feel the need to discuss them. This explanation was suggested by Pardon et al.,[159] who found in their study that cancer patients and their relatives were significantly less often involved in end-of-life decision-making than were non-cancer patients. The differences in involvement between patients with and without cancer were found to be predominantly attributable to 'intensifying the alleviation of pain and symptoms', a relatively standard practice in modern oncological care. Such decisions may be made without active involvement of the patient.[170] Nonetheless, conforming to the principle of patient autonomy – traditionally one of the main principles within medicine and an ethical imperative of decision-making at the end of life –[171] all possibly life-shortening practices must be discussed with the patient, unless he or she has specifically expressed otherwise.[172] The findings of this dissertation underscore the importance for physicians and other healthcare providers to keep encouraging patients to be active participants in the process of decision-making.[91] Yet caregivers should bear in mind that people vary in their specific preferences for the degree of participation in treatment decisions near the end of life.[173] Physicians should be aware of these preferences and individually tailor the process so that patients can co-decide to the extent they are willing to be involved in shared decision-making.[91,148]

While respecting the patient's wishes is paramount in decision-making, the patient's relatives can make important contributions to decision-making too.[159,174] As stated by the World Health Organization (WHO), palliative care should aim to improve the quality of life of *both patients and their relatives* who are confronted with life-threatening illness.[175,176] Therefore, involving relatives and other important people close to the dying patient in decision-making is regarded as good medical practice for physicians and other healthcare professionals.[124,177] Shared decision-making and adequate, timely communication with both patients and families can improve mutual understanding between patients, families and physicians,[178,179] optimize the end-of-life experience,[180] positively affect surviving family members' psychological wellbeing (e.g., reduced likelihood of depression and anxiety) and enhance post-bereavement adjustment.[164,181]

The involvement of family members in decision-making becomes, of course, more important when the patient becomes incompetent. Our findings (**Chapter 6**) showed that where the patient was lacking in competence, relatives were involved in the decision-making process in less than 70% of cases (in all cancer types, except for breast cancer where this percentage was slightly higher). Given that prior research has shown that the vast majority of cancer patients want their families involved in medical decisions near the end of life, specifically in case of loss of competence,[159] our study's results indicate that there is still room for improvement. Also remarkable was the very low rate of written advance directives (less than 6%) in patients without decisional capacity. It is important for physicians to openly talk about ELDs and involvement preferences with advanced cancer patients and their families. Advance care planning (ACP), which includes ongoing discussions with loved ones and surrogate decision-makers, as well as advanced directives which spell out patients' preferences concerning medical treatment should they lose decision-making capacity, can be helpful.

High occurrence of euthanasia or physician-assisted suicide in advanced cancer in Belgium

Our results showed that the occurrence rate of ELDs was equally high in the five most common cancers (gastrointestinal, respiratory, genitourinary, breast, hematological), which may suggest that oncologists and cancer patients see potentially or certainly life-shortening medical practices as acceptable options at the end of life. More than one in ten cancer deaths (10.4%) registered in 2013 were from euthanasia or physician-assisted suicide. This is an important rise if we compare this percentage with the 5.6% of all cancer deaths due to euthanasia registered in 2007,[182] and to the general (not only cancer deaths) rate of 4.6% registered in 2013.[36] The findings led us to conclude that assisted dying practices are widespread within cancer care in Belgium. In general, cancer patients appear to have equal opportunities to access and go through the procedures of euthanasia, regardless of their specific cancer diagnosis. On a societal level, this is an indication that assisted dying is fairly well imbedded in care at the end of life of cancer patients. Of course, end-of-life decisions are strongly related to the healthcare system and the regulating framework within a country. Belgium was the second country in Europe after the Netherlands to legalize euthanasia, in specific circumstances and subject to statutory safeguards. The Belgian Act on Euthanasia went into effect in September 2002, decriminalizing the intentional ending of a competent patient's life by a physician at the patient's explicit request.[183,184] The seemingly broad integration of euthanasia in end-of-life care for cancer patients in Belgium may have been a consequence of the training and clinical support of medical professionals by the 'Life End Information Forum' (LEIF) physicians,[185] but also of the continuous debate about euthanasia in the media since legalization, which can have made it less of a taboo and may have led to increased awareness of the rights of the terminally ill and to an increase in the acceptance of euthanasia in general.[186]

However, it is important to note that there is little evidence on how well euthanasia is integrated in palliative care in Belgium. Moreover, the relationship between euthanasia and palliative care can go both ways. Good palliative care could possibly reduce the numbers of requests by patients, but it could also lead to an increased request for euthanasia by terminally ill patients. In the first scenario, proper symptom control can lead to less suffering, and consequently, the urgent need for ending life might disappear until the suffering becomes unbearable again. But good palliative care means also very good communication skills and ideally it includes existential caregiving. The latter might create a safe environment and relationship between physician and patients, thereby possibly taking away important barriers to talk about euthanasia.

7.3.4 The relevance of this dissertation in light of recent advances in cancer therapeutics

The findings presented in the various chapters of this dissertation are based on data collected from 2015 to 2018 (**Chapter 2:** ***ACTION study***), 2011 to 2013 (**Chapter 3:** ***EPCCS study***), 2009 to 2010 and 2013 to 2014 (**Chapter 4:** ***EURO SENTIMELC study***), 2014 to 2016 (**Chapter 5:** ***QPAC study***) and 2013 (**Chapter 6:** ***ELD study***). Thus, for four out of five chapters, data collection occurred more than five years ago.

Over the past ten years, significant progress has been made in cancer therapy. Immunotherapy, a type of treatment that works by strengthening the body's own immune response to identify and eliminate cancer cells, has developed rapidly, and has already demonstrated impressive efficacy in the treatment of multiple malignancies, including metastatic lung cancer.[187,188] Alone or in combination with conventional treatments such as chemotherapy, immune-based therapies can prolong life in people with advanced-stage cancer.[189] This does, however, not diminish the importance of (timely) palliative care involvement for this patient group, which should be based on what they *need*, independent of prognosis or treatment intention, as recommended by the *Lancet Oncology* Commission paper 'Integration of oncology and palliative care' (2018).[43] People who are surviving for long periods of time may be in an incurable state for many years, with great variations in their need for palliative care.[43] Research has shown that patients may experience physical, emotional and existential distress – which are key concerns of palliative care – during the life-prolonging phase of cancer treatment.[123,190] Regardless of the recent developments in cancer therapies, optimizing QoL (assessed using patient-reported outcomes (PROs) and relieving suffering remain primary goals of treatment.

The WHO also formulates palliative care as an approach in which oncology care and palliative care are integrated or given in parallel. '*… It is applicable early in the course of the disease, in conjunction with other therapies that are intended to prolong life.*'[191] Palliative care needs should therefore, as a rule, be assessed as an ongoing process *from the point of diagnosis onwards*.[43] When cancer treatment and palliative care are provided simultaneously, patients benefit from the expertise of both oncology and palliative care teams. This is extra important in this era of novel cancer therapeutics, because immune-based therapies have a lower toxicity than standard cancer treatments, making them more suitable for people closer to the end of life.[192] When treatment is aimed at cure or prolonging life, most care for people with life-threatening illness can be provided at the generalist level by healthcare professionals with basic competence in palliative care – in this context mainly from oncologists – at any moment in time, from diagnosis to the end of life (e.g. performing careful and systematic symptom assessment to identify patients who are in need of specialist palliative care, informing patients and families adequately about prognosis and treatment options).[193] As many cancers are becoming more chronic in nature, generalist primary care providers such as GPs and community nurses are also increasingly being recognized as having a central position in cancer control.[194] In challenging circumstances or when patients suffer from complex symptoms, generalist caregivers will seek advice from, or refer to specialist palliative care services.

7.4 IMPLICATIONS AND RECOMMENDATIONS

The following sections outline implications of the findings described in this dissertation, for future research as well as for clinical practice and policy in relation to end-of-life care in advanced cancer.

7.4.1 Challenges and directions for future research

Research conducted within the context of a doctoral project may be limited by time and costs, but science is a never-ending process. Obtained results typically bring another set of new questions and thoughts to light that can serve as a reference point for future work. Based on the studies in this dissertation, below some suggestions and possible avenues for future research are outlined that remain to be further explored and more exhaustively studied.

1) Investigate in depth the reasons for cross-country variation in important patient-reported outcomes in cancer

Healthcare professionals and policy makers in cancer care share the same critical goal: assuring that people with cancer who need healthcare services receive the best possible care, in the right place and at the right time, sensitive to their needs and preferences. Nonetheless, improving quality of cancer care has proven to be a serious challenge for many nations, and substantial differences in care outcomes persist across countries[71] Our results (**Chapter 2**) underline this, as we found some clear variations in patient-reported functional status, symptom severity and QoL across patients living in different countries. There are numerous factors that could possibly contribute to these findings. For instance, differences may reflect heterogeneity in national health systems and healthcare organization (e.g., the availability of and access to health services) across countries. In addition, or alternatively, variety may be due to cultural practices and attitudes (e.g., different attitudes towards pain relief).[17,195] The design of the present study did not allow for drawing firm conclusions about underlying systemic reasons. Since a better understanding of these reasons and explanations might guide eventual courses of action, we believe that this is an essential area of further research. Cross-national comparative research enables countries to learn from each other with the goal of improving their cancer policies. Policy makers can use outcome data as an instrument to identify areas to work on and to recognize strong points. It will be useful for future comparative studies to have a thorough look at the available healthcare services in different countries across Europe, for example by exploring the roles of generalists and specialists in the delivery of palliative care. More research will also be needed to examine how differences in education, financing, attitudes and national cultures of palliative care relate to inter-country variations in patient-reported outcomes and (end-of-life) care quality or efficiency in advanced cancer.

2) Conduct longitudinal research to identify those factors that predict important patient-reported outcomes and their evolvement over time

Relieving suffering as much and as early as possible is a central component of palliative cancer care. Hence, a clear understanding of factors associated with patient-reported functioning, symptom and QoL improvement is required to provide patients with advanced cancer with optimal symptom management. Due to the advances in cancer therapy over the past few decades, more and more people are surviving for an extended time course with cancers that are considered incurable. During their cancer journey, usually characterized by a slow decline over a period of many months or even several years, these individuals have to deal with difficult continuing challenges in setting and shifting personal goals and in planning their care to achieve these goals.[196] This is why longitudinal research designs involving prolonged time frames and large amounts of data are so important: they allow us to recognize and determine certain patters that shorter term research does not.

In this dissertation, we described the course of emotional functioning, physical functioning and symptom intensity over time in palliative care cancer patients (**Chapter 3**). The findings showed that people may experience unfavorable changes in self-reported functional status, symptom intensity and overall QoL at several different points in time towards the end of life. Our research was explorative in nature and did not specifically investigate factors associated with the evolution of these patient outcomes over time. We could therefore not determine what could characterize patients with different levels of functional impairment, symptomatology and QoL (e.g., low, medium, high) throughout the course of the illness towards death. This highlights the need for further prospective studies to identify those factors that predict which patients are most at risk of high symptom burden, and that can be targeted to prevent poor patient outcomes. While that may sound evident, limited information is available concerning longitudinal assessments of symptoms and their determinants.Increased scientific knowledge on changes in functional status, symptoms and QoL throughout the disease trajectory and how they are related to cancer-related treatment could help support healthcare professionals in deciding when and where palliative care needs to be strengthened and in selecting appropriate interventions to guide patient care.

3) Study advance care planning among cancer patients and different healthcare professionals throughout the illness trajectory

Patient-centered communication and advance care planning (ACP) have received increasing policy attention in Europe over the last years. In this dissertation, we looked at trends in the prevalence of GP-patient conversations about certain end-of-life topics (diagnosis, options for palliative care, psychosocial problems, GPs' awareness of patient wishes about a medical treatment that he/she would or would not want in the final phase of life, GPs' awareness of patient wishes about who was to make decisions regarding medical treatments or activities in his/her place, in the event he/she would no longer be able to speak for him/herself (proxy decision-maker)) in three European countries (**Chapter 4**). Our findings seem to be generally consistent with recent heightened attention to good communication and to initiatives to increase the uptake of ACP in Europe. However, our study only reported if topics were discussed according to the GP, and this does not represent the full complexity of end-of-life communication with cancer patients. ACP is a broad concept involving multiple stakeholders. Due to the ongoing increase in the specialization of cancer care and palliative care, it may be that certain topics are more often discussed with palliative caregivers rather than with GPs. Future research should provide a more complete picture by incorporating the ACP process as a whole and including the perspectives of patients and their families, as well as the various involved healthcare providers at all healthcare levels. It would be interesting to follow patients throughout the trajectory of their illness across multiple care settings to evaluate, for each patient and their family caregivers, the total process of communication and ACP. It may, for example, be valuable to explore the continuity of the ACP process throughout the cancer care trajectory, which, as far as we are aware, has never been well studied.

7.4.2 Implications and recommendations for clinical practice and policy

Throughout this dissertation, we identified several relevant focus areas in palliative cancer care. In the sections below we delineate some important implications and recommendations for practice and policy.

1) Incorporate routine assessment of patient-reported outcomes into clinical practice as standard part of cancer care throughout the illness trajectory

Our findings (**Chapter 2** and **Chapter 3**) confirm that the optimization of symptom control, functional status and QoL remains a challenge to healthcare workers in palliative cancer care across European countries, and that this becomes even more difficult in later stages of the disease trajectory, as the illness progresses towards the end of life. We strongly emphasize the importance of including periodic subjective, patient-reported outcomes assessments as part of healthcare providers' routine ways of working in cancer care. In the first place, this might be done in oncology departments or clinics or in primary care practices, but a more thorough assessment could be performed by specialist palliative care services or psychosocial oncology teams if necessary.[43]

Patient-reported outcome measures (PROMs) are increasingly used in clinical settings for tracking symptoms, needs and progress of individual patients over the course of care.[197] The repeated, systematic administration of PROMs to direct patient care has a range of benefits. Besides aiding early detection and treatment of symptoms and other health-related issues of priority,[198] routine collection of patient-reported outcomes may help health professionals achieve competency in being responsive to patients' needs throughout the whole cancer illness trajectory,[11,12,199] for example by estimating the most appropriate moment to refer to palliative care services.[200] When applied in routine medical consultations, PROMs may foster patient-physician communication and patient engagement in shared decision-making.[199,201-204]

Unfortunately, despite their benefits, PROMs are rarely embedded as part of routine oncological care.[205-207] Common barriers that get in the way of effective integration of PROMs in daily practice include time constraints, a lack of knowledge on what type of PROMs may be suitable for this purpose, a lack of knowledge on how to use them and interpret the scores, absence of proper data collection infrastructure and challenges more generally related to organizational change processes.[208-211] Overall, we feel that a more comprehensive understanding of elements affecting successful implementation of PROMs is needed. This would require increased time investment and resources in appropriate training for healthcare providers on how to incorporate patient-reported outcomes in daily cancer care, throughout individual patients' trajectories.[212] Advances in technology have resulted in the development of electronic systems to facilitate the collection and reporting of patient-reported outcomes across settings.[197] In the influential *Lancet Oncology* Commission paper 'Integration of oncology and palliative care' (2018) – which also recommends implementation of the routine use of PROMs in all settings – the authors argue for the use of electronic questionnaires, e-PROMs. Electronic PROMs allow for immediate display of interpretable results to the clinician and easier storage and transfer of patient results, which facilitates communication and information transmission during consultations. Patient scores can be integrated with other clinical data into electronic patient records.[43] These developments will bring new opportunities to the implementation process.

2) Facilitate strong, collaborative relationships among different professions across care settings in order to support information sharing and continuity of care

Multiple care providers and settings are needed to deliver good palliative cancer care and to provide good comfort care and symptom control for people with cancer. Palliative care thus has by definition a multidisciplinary nature. Consequently, collaboration and coordination of care can be complex. It involves numerous disciplines and transitions between different locations and levels of care throughout the disease trajectory. Coordination of care also implies good interprofessional cooperation. Effective, systematic interprofessional collaboration and integration of services is of major importance in facilitating efficient transitions and a smooth 'flow' of oncology patients, information and resources between inpatient, outpatient and home settings.[213]

This dissertation looked at several types of care settings and services. Each type of service has an important role to play, and has its own strengths and weaknesses. It is known from previous research that the link between primary and secondary care in the follow-up of patients with cancer is not optimal. The decreasing trends in GP-patient conversations about options for end-of-life care and psychological or social problems reported in **Chapter 4** of this dissertation seem to suggest that there might be a weakness in collaborative relationships and communication or information sharing between general practice and specialist practice. In order to preserve an effective doctor-patient relationship and ensure continuity of care, GPs should be more proactive in maintaining contact with their patients after diagnosis.[214] At the same time, specialist carers should take responsibility for keeping GPs informed of their patients' care. The multidisciplinary hospital team could provide GPs with complete and timely information so that they can keep supporting their patients through the different phases of their cancer journey. Collaboration could be further facilitated by use of electronic health records, which will likely improve GPs' access to patient information and enhance information transfer among the generalist and specialist care setting.[43,215]

In **Chapter 5**, focusing on specialist palliative care in Belgium, we demonstrated that cancer patients' and bereaved relatives' evaluations of information provision were substantially more positive in cases where the patient received care within a separate hospital-based PCU (where care professionals are available 24/7 to provide highly individualized care) compared to cases where the patient received care from a hospital-based mobile palliative support team or a mobile palliative homecare team (which act mainly as consultants, providing guidance at the request of other healthcare professionals). This implies that the support provided in the PCU setting could be used as a performance 'benchmark' by other specialist services – ideally, we should be able to reach the same level of provision across all these services. Transferring techniques and routines used by PCUs to other care settings may, however, not be easy due to constraints in time, staff and resources. In order to improve care and to make it possible for professions to learn from each other's best practices, creating and nurturing optimal cooperation and collaboration between healthcare providers is an important area of attention for policy makers.

3) Invest in education and training for future and current health workers in palliative cancer care to promote interprofessional collaboration

The previous recommendation highlighted the need for strong, collaborative relationships among healthcare providers from different care settings as a key factor for sustaining continuity of care in cancer care throughout active treatment, supportive care, palliative care, survivorship or end-of-life care. Interprofessional collaboration is a fundamental competence that needs to be strongly supported at policy level, and this calls for increased educational efforts. To improve cancer care throughout the full care trajectory on a larger scale, interprofessional cooperation needs to be given more attention and should be sufficiently integrated into the curricula of all basic (e.g., medical school, nursing school, social work) and specialized, post-graduate education (e.g., for GPs, oncologists, palliative care physicians, oncology nurses). Interprofessional training needs to be properly integrated into the existing palliative care trainings. In many countries these palliative care programmes are still failing to equip healthcare and social professions with the specific attitudes, knowledge and skills to work effectively together to deliver high-quality palliative care. Interdisciplinary collaboration needs to be trained and not regarded as something that will be developed on the job. An example could be communication training on bad news, especially in the context of cooperation: as a care team, with everyone involved, how do you act, how can you deal with bad news or with end-of-life wishes? How could you for example prevent that the GP knows and addresses what the patient wants, but the oncologist does not? These competencies should be incorporated into training at medical school, but can also be addressed after graduation during interprofessional workshops.

4) Implement strategies to improve the engagement of patients and family in end-of-life decisions that may hasten the patient's death

Patient-centered care is the practice of caring for patients and their families in a way that is 'respectful of, and responsive to individual patient preferences, needs and values, and ensuring that patient values guide all clinical decisions,' as defined by the Institute of Medicine (IOM) in its 2001 landmark report.[216] Patient involvement in medical decision-making is considered a crucial component of patient-centered care and becomes even more vital when a patient approaches the end of life. The majority of cancer patients want to be involved in decisions about end-of-life care.[135,137,140,141,165] Nevertheless, as described in **Chapter 6**, we found that according to their physicians, 20% of competent cancer patients (i.e., those who were judged to have decision-making capacity) were not involved in the decision-making process preceding end-of-life decisions (ELDs). ELDs are those decisions made at the end of life that potentially or certainly shorten life and that are frequently made in the case of people with incurable cancer. Whereas our numbers are an improvement as compared to those of a previous study in 2011 in which 50% of advanced lung cancer patients were barely or not at all involved in end-of-life decision-making – regardless of the preferences of most of them,[159] this is still one in five patients who are not involved where they *could* be. Likewise, less than 70% of relatives were involved in the decision-making process in cases where the patient was deemed incompetent, while it is known from earlier work that most people with cancer prefer their family members to take part in medical decision-making near the end of life, especially when the patient lacks decision-making capacity.[159]

There are several barriers for healthcare professionals to actively engaging patients and their families in end-of-life decision-making, such as professional caregivers' or patients' (perceived) resistance to doing so, not having enough opportunity or time to talk to those people, a lack of training received by healthcare professionals, a lack of understanding of the important role of relatives, not being aware of who to talk to, or not being able to get in touch with the right people quickly enough in an urgent situation.[166] The assignment of a 'proxy', a central family caregiver who has a direct line of communication with the patient's physician to discuss their loved one's care and treatment if the situation calls for it, should be part of standard cancer care. It is imperative to ensure that up-to-date emergency contact details and back up contact details are on file from early on in the disease trajectory, and that this information is accessible to multiple professional caregivers. With the increased complexities in therapeutic interventions in cancer care, it is more important than ever to focus not only on the increase in cancer survivorship, but also on quality of life and the patient-centeredness of care and decision-making processes. For policy makers it is useful to closely monitor the evolution of patient and family involvement in end-of-life care and ELDs over time. Possible changes over time would inform healthcare providers and healthcare managers whether they need to take action, for example by enhancing education and processes, in hospital settings as well as outside the hospital setting. The organization of the healthcare organization should be such that patients and relatives have the opportunity to play a more active role in their care, treatment and support throughout the entire cancer journey (diagnosis, treatment, palliative care, end-of-life care), taking into account their own, unique wishes.

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Part IV

Appendices

S

English summary

INTRODUCTION

Background

Changes in patterns of death and dying

The dying experience and the way in which people deal with death and dying have not always been the same. A century ago, death often came abruptly and primarily as a result of infection, accidents or childbirth complications. Due to improved public health, medical knowledge and technology – and therefore an increasing life expectancy and growing population of elderly over the past century, mortality rates from acute causes declined and have been gradually replaced by a rising number of deaths attributable to 'non-communicable' diseases, with the largest two being cardiovascular disease (estimated 17.9 million deaths per year worldwide) and cancer (estimated 9.6 million deaths per year worldwide). These diseases tend to have more prolonged illness trajectories, with a functional decline over months or years.

Changes in perspectives on the care for dying people

The modern hospice movement, founded in the 1960s by Dame Cicely Saunders (1918-2005), was an important marking point in the care for dying and incurably ill people and laid the groundwork for and further developed into the contemporary concept of palliative care. In the 1970s palliative care came to be synonymous with the physical, psychosocial and spiritual support of patients with life-limiting illness, provided by a multidisciplinary team. Palliative care focuses on maintaining comfort and quality of life for those facing multiple, complex problems over longer periods of time. It supports preserving a sense of dignity and control over one's life circumstances, especially in the later stages of a disabling, progressive illness.

Palliative care and end-of-life care in people with advanced cancer

Growing population of people with advanced cancer

Cancer incidence and mortality are rapidly growing across the world due to a growing and ageing population and a changing prevalence and distribution of certain cancer risk factors, such as diet and physical inactivity. Although advanced cancer usually cannot be cured, treatments may help slow the progression and extend people's lives for months or even years. The rising cancer incidence and prolonged survival of patients with advanced-stage illness place increasing pressure on populations and healthcare systems across the globe, and go along with a growing critical public health need for high-quality palliative care and end-of-life care services.

Palliative care

Palliative care starts from the understanding that every patient has his or her own story, relationships and culture, and that he/she deserves respect as a unique individual. This respect includes providing the best available medical care, so that people can live their lives as fully and comfortable as possible. One of the most widely used and cited definitions of palliative care was formulated by the World Health Organization (WHO) in 2002: 'Palliative care is 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 the relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.' The WHO definition continues by adding some core principles, including providing relief from pain and other distressing symptoms; affirming life; and regarding dying as a normal process, intending neither to hasten nor postpone death. Palliative care uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated. Palliative care can enhance quality of life, and may positively influence the course of illness.

Historically, palliative care originated in the oncology setting as care for cancer patients nearing the end of life. Today, cancer patients remain the largest disease group receiving palliative care in many countries. While the focus was originally on terminal cancer patients for whom all active treatments had ended, it is now widely acknowledged in research, practice and policy that palliative care is not limited to terminal disease. Nowadays, a 'trajectory' model of palliative care is used, which integrates curative/life-prolonging therapy and palliative care. Palliative care is introduced when a life-limiting illness such as cancer is diagnosed, and becomes increasingly important as the illness progresses, responsive to individual patient needs and preferences. The initial emphasis on curative treatments decreases gradually and shifts to an emphasis on relief of symptoms and psychosocial support for patients and their caregivers.

End-of-life care

The terms 'palliative' and 'palliation' are often equated with the provision of end-of-life care; however, palliative care and end-of-life care are overlapping but not identical concepts. Palliative care includes care provided at the end of life, but also entails much more from time of diagnosis until death. End-of-life care more narrowly refers to care occurring in the final phase of a patient's life, generally in the last couple of months. The time frame of the end-of-life period depends strongly on the underlying diagnosis and clinical course and is of course difficult to predict in many cases. In the context of this dissertation, we opted for a pragmatic definition of end-of-life care referring to all care directed towards the treatment and support of people with advanced cancer who are nearing the end of their life, regardless of whether the care one receives is palliative in nature or life-prolonging.

Providers of palliative and end-of-life care: generalist and specialist palliative care

Regardless of the care setting, palliative care can be provided through skills at the generalist level and at the specialist level. Although palliative care is not infrequently misconceived as only referring to specialist palliative care, not every person needs a specialist to receive appropriate care, and most care for people with life-threatening illness and those nearing the end of life occurs in a primary care setting. An appropriate combination of generalist and specialist palliative care is a more sustainable and cost-effective solution for optimal coverage of the population in need of palliative care than providing specialist palliative care in all situations.

Generalist palliative care is typically provided by regular caregivers who have some clinical experience and basic training in palliative care, but who do not have a core identity as palliative care provider. In many countries, general practitioners (GPs) are the main providers of generalist palliative care. Other examples of generalist palliative care providers are oncologists, nursing staff and social workers. In complex and challenging circumstances, these caregivers will seek specialist advice or offer referral to secondary specialist palliative care services.

Specialist palliative care providers are professionals whose prime responsibility is the provision of palliative care. They have obtained expert knowledge, competences and specific formal training to serve the goals of palliative care. Specific roles and tasks vary by country; in most countries specialist palliative care is provided in the context of a specialist multidisciplinary team dedicated to palliative and end-of-life care. When such a team is involved, patients usually continue to receive ongoing care from their main physician or clinical team, although a patient can be referred to a specialist team for continuous care in particularly demanding cases. Evidence from previous work shows that cancer patients have higher chances of using specialist palliative care services than patients with non-cancer diseases, and that cancer patients are referred earlier to specialist palliative care.

Palliative care in medical oncology

In its position paper on supportive and palliative care, the European Society for Medical Oncology (ESMO) Supportive Care Faculty emphasizes that the multidisciplinary team caring for patients should ensure that patients can voice their needs, which may vary depending of the stage of the illness and will often evolve over time. ESMO states that 'more and better scientific evidence [...] is required so that effective interventions can be proposed to cancer patients at each stage of their illness.'

The white paper of the European Association for Palliative Care (EAPC) also mentions the provision of suitable information about the illness, treatment and care options; support in individual care planning and decision-making; good communication skills; priorities/dimensions of quality of life (which can shift when the disease progresses); and a multidisciplinary approach as being common and important principles of palliative care.

In the United States, the American Society of Clinical Oncology (ASCO) and the American Academy of Hospice and Palliative Medicine (AAHMP) worked together in order to create a consensus definition of what comprises high-quality primary palliative care in medical oncology. Symptom assessment and management, communication, advance care planning and end-of-life care were endorsed as the most important domains of palliative care.

The 2018 *Lancet Oncology* Commission paper provides recommendations from a large international expert commission on how to strengthen the integration on oncology and palliative care. The paper argues that routine assessment, the use of patient-reported outcomes (PROs) and active patient participation in decision-making about cancer care contribute to better symptom control, better physical health and mental wellbeing and improved use of health-care resources. Significant barriers to effective integration are a lack of international agreement on the content and standards of organization, education, and palliative care research in oncology. The Commission calls for rethinking and reorganization of cancer and palliative care delivery to promote collaboration at different care levels and to improve treatment. This integrated model must be reflected in international and national cancer care plans.

The above examples illustrate that symptom management and patient-physician communication continue to be considered foundational skills that healthcare professionals need to help patients with advanced illness as well and fully as possible, and that are central to the successful development and implementation of integrated palliative care strategies.

Symptom burden and quality of life

Cancer-related symptoms

People with advanced cancer frequently experience devastating symptoms arising from the illness itself and its progression or from cancer treatment, which may gradually get worse over time and interfere with everyday functioning. Advanced cancer also has a profound impact on mental health, with many patients suffering from the emotional effects of their illness, such as depression and anxiety. Cancer symptoms and quality of life issues are – and should continue to be – among the highest priorities of oncology clinicians and researchers, however, the fact that the prevalence of physical as well as psychological cancer-related symptoms remain high suggests that these symptoms are not always adequately managed.

Quality of life

Increasing overall survival has long been the primary focus of cancer treatment, but it is now generally acknowledged that preserving quality of life (QoL) is a very important endpoint and a major goal for patients with advanced cancer. QoL has been defined by the World Health Organization (WHO) as 'an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, standards and concerns […] affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment.' Monitoring cancer-related symptoms and QoL is crucial to enable healthcare providers to better react to patients' changing needs.

Symptom burden and quality of life across countries and over time: need for further research

Maintaining or improving QoL and providing relief to patients from distressing symptoms are crucial outcomes of palliative care. Adequate monitoring of these outcomes is needed to inform and guide person-centered care. To better understand symptom burden and QoL in advanced cancer patients and plan more effective symptom management, there is a need for more knowledge about the experience of symptoms from the patient's perspective. Since contextual factors such as cultural, ethical and legal context and aspects of healthcare systems vary between countries, studying cross-national differences in symptom burden and QoL could be useful for a better understanding of how people with advanced cancer are cared for across European countries, and for identifying possible areas for improvement. Furthermore, because good-quality palliative requires optimal symptom control and support at *any* point along the advanced illness trajectory and towards the end of life, it is important to assess functional status, symptom burden and QoL not only cross-sectionally but also over an extended period of time.

Communication and information provision at the end of life

Patient-centered communication and the discussion of end-of-life topics

Good-quality palliative care requires that physicians engage in patient-centered communication, which involves respecting the patient as an individual, directing patients to the care they need when they need it, providing timely, adequate and understandable information, supporting involvement in decision-making and making decisions consistent with patients' values. There are many advantages of effective communication, including better understanding of the illness, care and treatment options, adherence to therapeutic regimens and satisfaction with end-of-life care. Nonetheless, multiple barriers exist in communication with patients and their families, including a general reluctance to talk about death and dying or lack of knowledge and training in this area. Over the last few decades there have been consistent findings that cancer services do not always meet patients' needs for communication, information and support. Poor communication can have significant consequences such as adverse mental health outcomes, worsening of symptoms, and more aggressive, unwanted life-prolonging care. There is little comparable, empirical evidence on the content and frequency of end-of-life care communication practices among people with cancer in Europe. Contextual circumstances such as culture, healthcare system organization, resource ability or attitudes towards the end of life may affect such practices.

Information provision and shared decision-making

Enabling people to make informed choices about their own care and provide care that is in line with a person's preferences have been core values of palliative care since its inception. To be active participants in their care, patients and their families must have an adequate understanding of their illness, treatment and care options. While personal values and capabilities should always be taken into account when tailoring (the amount of) information to patients and when engaging people in healthcare decision-making, the clear majority of cancer patients today report a preference for detailed information about their condition and approximately two-thirds want to be actively involved in decision-making about their care. Likewise, information provision to family members plays an important role, as family are involved in medical decision-making in many cases and may become the key communicators with healthcare and palliative care professionals when a patient is no longer able to do this themselves. With their specific training in supporting patients in the final phase of life, it would be expected that specialist palliative care providers pay a considerable amount of attention to optimizing the provision of information to their patients, and that those being guided by specialist palliative care services are given the opportunity to be actively involved in decision-making. As far as we know, research to date has not yet investigated the provision of information – also regarding end-of-life care – to cancer patients and those close to them by different types of specialist palliative care services.

End-of-life decision-making

Potentially life-shortening end-of-life decisions

When death approaches, the goals of medical care need to be adjusted. The patient's comfort is more than ever key to all decisions about treatment and care. Efforts to improve the patient's comfort can lead, though rarely, to the (possible) hastening of death, mostly as a foreseen but unintended consequence of decisions to refrain from potentially life-extending but burdensome interventions or to use highly dosed medication to relieve severe pain. In some occasions, hastening of death may be an appreciated or even explicitly intended outcome, when the patient is experiencing unbearable suffering with no prospect of improvement. Former research has shown that end-of-life decisions with a possible or certain life-shortening effect (ELDs) are more prevalent in cancer patients than in non-cancer patients, possibly due to a higher symptom burden in cancer and the better availability or accessibility of palliative care services. ELDs in cancer patients have been described by several prior studies, but to our knowledge, none have investigated the occurrence of ELDs and characteristics of the decision-making process across cancer types. It is known from earlier studies that patients with different types of cancer do not always receive the same types and intensity of end-of-life care. If such variation across cancer types also exists regarding the prevalence of ELDs and aspects of the decision-making process, this might be an indication of inequity in the provision of end-of-life care to people with advanced cancer.

STUDY OBJECTIVES

Three objectives, each with specific research questions, guide this dissertation.

The ***first objective*** (**PART I**) is to evaluate self-reported emotional and physical functioning, symptoms and quality of life in people with advanced cancer. The research questions are:

1. What is the patient-reported emotional and physical functioning, symptom intensity and overall quality of life in people with advanced cancer in six European countries, and are there differences between countries? (**Chapter 2**)
2. How do patient-reported emotional and physical functioning, symptom intensity and overall quality of life differ between cancer patients receiving palliative care in Europe, and how do these outcomes progress over time? (**Chapter 3**)

The ***second objective*** (**PART II**) is to evaluate end-of-life communication and information provision in people with advanced cancer. The research questions are:

3. Are there trends over time in communication about end-of-life topics with cancer patients in general practice in three European countries, and are there differences in time trends in GP-patient end-of-life communication with respect to the patients' age at death, gender, cancer type, place of residence in the last year of life and place of death? (**Chapter 4**)
4. How do people with cancer being supported by specialist palliative care services evaluate information provision and their involvement in decision-making, how do bereaved relatives of cancer patients who received care of specialist palliative care services evaluate information provision, and do these evaluations differ depending on patient characteristics, length of guidance and the type of palliative care service? (**Chapter 5**)

The ***third objective*** (**PART III**) is to examine end-of-life decisions and the preceding decision-making process in people who died from cancer. The research question is:

5. What is the prevalence and what are the characteristics of end-of-life decisions in different cancer types? (**Chapter 6***)*

METHODS

Different data collections were used to address the study objectives and research questions of the dissertation.

Cross-sectional survey among people with advanced cancer: baseline data from an international multicenter cluster-randomized trial among people with advanced cancer (Chapter 2)

To address ***research question 1***, we used baseline patient data from the *ACTION trial*, a multicenter cluster-randomized controlled trial carried out in 23 hospitals in six European countries (Belgium, Denmark, Italy, the Netherlands, Slovenia, United Kingdom) from 2015 to 2018. Per country and per pair of comparable hospitals (academic or non-academic), hospitals were randomized to either the intervention arm, providing 'usual care' supplemented with a structured advance care planning (ACP) program, or to the control arm, offering 'usual care' only. Competent patients with advanced lung (stage II or IV) or colorectal cancer (stage IV) or metachronous metastases who were deemed eligible by members of their healthcare team informed of the study and invited to participate. Lung and colorectal cancer patients were selected for the study because these cancers have high incidence and death rates in Europe and affect both sexes.

Patients were followed until one year after entering the study. They were asked to complete a questionnaire at baseline – i.e., the moment of inclusion, prior to delivery of the ACP program to the intervention group – and again at 11-12 weeks, and 19-20 weeks post-inclusion. Only baseline data are reported in the study included in this dissertation. Treating physicians or other healthcare professionals delivered clinical background information. All relevant outcome variables were assessed using the palliative care version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C15-PAL). This measurement tool is a shortened version of the EORTC QLQ-30 core questionnaire for measuring QoL in cancer patients.

International multicenter longitudinal study among people with cancer enrolled in palliative care (Chapter 3)

We drew on data from the multicenter longitudinal *European Palliative Care Cancer Symptom (EPCCS) study* in order to answer ***research question 2***. The EPCCS study was conducted between April 2011 and October 2013 in 30 palliative care centers in 12 countries (Australia, Belgium, Canada, Denmark, Georgia, Germany, Italy, Norway, Portugal, Spain, Switzerland and United Kingdom). A large number of patients with advanced, incurable cancer enrolled in a palliative care program were included. Patients receiving treatment with curative intent were excluded.

The data we used were collected through a case report form on medical data completed by healthcare providers (HCP-CRF) and by participants' self-report on health and symptoms (patient-CRF). Both CRFs were completed monthly (3-5 weeks) for a minimum of three months, or until death or study withdrawal. The HCP-CRF consisted of a brief set of medical and treatment-related variables, e.g. primary cancer diagnosis, comorbidities, anti-cancer treatment and medications. A retrospective recording of date of death was performed in each study center approximately six months after the last study inclusion. The patient-CRF consisted of key socio-demographic characteristics, e.g. age, gender, marital status, living situation and education (collected at baseline), and questions on quality of life (QoL) and symptom severity. The variables of interest in our case were overall quality of life, emotional functioning, physical functioning and cancer-related symptoms as assessed by the palliative care version of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C15-PAL).

Mortality follow-back study among general practitioners (GPs) of cancer patients in representative epidemiological surveillance networks (Chapter 4)

The data used to address ***research question 3*** were collected in Belgium, the Netherlands and Spain as part of the *European Sentinel Network Monitoring End-of-Life Care (EURO SENTIMELC)* study. The EURO SENTIMELC study is an ongoing mortality follow-back study designed to retrospectively monitor end-of-life care in population-based samples of deaths in different countries. The study was conducted in 2009-2010 (Spain: 2010-2011) and 2013-2014 among GPs in representative GP Sentinel Networks: nationally representative epidemiological surveillance networks consisting of GP practices or community-based physicians who continuously monitor health problems existing in the population. Participating GPs provided weekly reports on every adult patient in their practice who had died during the past week as part of a larger public health questionnaire. We included all people registered by the participating GP practices who died of cancer (coded according to ICD-10) whose death was not, according to the GP, 'sudden and totally unexpected'.

Using a standardized registration form consisting of structured and closed-ended items, GPs collected demographic characteristics and cancer type. Additionally, they reported for five end-of-life care topics (diagnosis, options for end-of-life care, psychological or social problems, the patient's preference for medical treatment and the patient's preference for a proxy decision-maker) whether they had been discussed with the patient.

Nationwide cross-sectional survey of 34 specialist palliative care teams (Chapter 5)

In order to examine ***research question 4***, we used data from a nationwide cross-sectional survey that was part of the more comprehensive *Quality Indicators for Palliative Care (QPAC) study*. Questionnaires were administered during four measurement periods (November 2014, May 2015, November 2015 and May 2016) within 34 specialist palliative care services (PCSs).

We used the survey questions related to information provision as evaluated by patients and relatives. Only those with a diagnosis of cancer were included in the analyses. Data from two different respondent groups were studied: 1) cancer patients being guided by PCSs at the time of the measurement, and 2) the people most relevant to patients who had died of cancer (e.g., partner, family member or friend most closely involved). People with cancer and bereaved relatives were identified based on the main diagnosis and on checklists that were completed by the coordinators of the participating palliative care teams. A cross-sectional inclusion method was used during every measurement period which required the palliative care teams to make a random selection of two groups of patients on the day of the assessment, with a maximum of 50 in each group: people who were under the guidance of PCSs on that specific day (patient questionnaire) and people who had died while under the guidance of PCSs between the previous four weeks and four months (bereaved relative questionnaire).

The questionnaire items related to information provision were either based on existing questionnaires or developed by the researchers in cooperation with an expert panel. Items were mainly derived from the CQ-index Palliative Care, a structured questionnaire containing questions on care experiences and consisting of a patient version and a relative version.

Nationwide retrospective survey among treating physicians based on death certificates (Chapter 6)

Data from the *death certificate study on end-of-life decisions (ELD study)* based on a representative sample of deaths in Flanders, Belgium, were used to address ***research question 5***. Between 1 January and 30 June 2013, a random sample of all deaths of Belgian residents (aged 1 year or older) was drawn weekly by the Flemish Agency for Care and Health (FACH). For our analysis all deaths in the database with an underlying cause of cancer were selected. Certifying physicians were sent a four-page questionnaire via standard mail within 2 months of the death concerning medical decisions made at the end of life, the decision-making process, and the care provided. They were requested to complete the questionnaire by consulting the patient's medical file. If the certifying physician was not the treating physician, the questionnaire was passed on to the treating physician.

Assuming end-of-life decision-making before death was not precluded (i.e. death had not been sudden and unexpected and the physician's first contact with the patient had been before death), physicians were asked whether they had (1) withheld or withdrawn life-prolonging medical treatment (e.g., chemotherapy, artificial provision of nutrition and hydration) taking into account or explicitly intending the hastening of death; (2) intensified the alleviation of pain and/or other symptoms with drugs with the possibility of hastening; or (3) administered, supplied or prescribed drugs with the explicit intention of hastening death. For patients for whom more than one ELD was made, the act with the most explicit life-shortening intention was regarded as the most important ELD. When two decisions with similar life-shortening intention were made, administering drugs was regarded as prevailing over withholding or withdrawing treatment as the most important ELD. Questions then followed about the reasons for the most important ELD and about the decision-making process. Data on sex, age, place of death, and underlying cause of death were available from the death certificate. The underlying cause of death variable was coded according to ICD-10.

SUMMARY OF THE MAIN FINDINGS

PART I: Self-reported emotional and physical functioning, symptoms and quality of life in people with advanced cancer

Patient-reported emotional and physical functioning, symptom intensity and overall quality of life in people with advanced cancer across European countries

In **Chapter 2** we studied emotional functioning, physical functioning, symptom intensity and overall quality of life (QoL) as reported by a large representative sample of people with advanced lung or colorectal cancer in six European countries. We also compared these outcomes across countries. Fatigue was the most severe self-reported symptom in this sample. The second- and third-highest scoring symptoms in terms of severity overall were insomnia and dyspnea. We found some commonalities in outcomes across countries. The difference in means between the highest and lowest scoring country was smaller than 10 points (often used as a threshold for clinical relevance) for pain, nausea/vomiting and constipation; thus, the scores for these three symptoms were laying relatively close to each other. Aside from similarities, the results also revealed international differences in symptom intensity, functioning and QoL. The most remarkable overall finding was that in general, the best scores (i.e., highest for emotional functioning and QoL, lowest for symptoms) were reported by patients from the Netherlands and from Denmark, while patients from the UK reported relatively less favorable outcomes. Patients from Belgium reported worse emotional functioning than the other countries averaged.

> The results underline the essential role of healthcare professionals to consistently monitor burdensome physical and psychological symptoms when caring for patients with advanced cancer. Policy makers must take into account cross-national differences in important patient-reported outcomes and invest in providing care tailored to the needs of their population. Future research should identify which factors are most important in causing these variations between European countries.

Patient-reported emotional and physical functioning, symptom intensity and quality of life in people with advanced cancer in Europe over time

In **Chapter 3** we investigated, in a large international sample of people with advanced cancer receiving palliative care, the course of functional status, symptom intensity and overall QoL over time. We performed a prospective analysis of the entire study sample, which illustrated that emotional functioning, physical functioning, symptoms and QoL remained generally stable from inclusion (baseline) over time throughout the study duration (≥8-month follow-up). Additionally, we conducted a retrospective analysis of participants who had passed away during follow-up. This approach revealed that emotional functioning remained initially stable (when comparing those ≥6 months prior to death with those 5-3 months prior to death), but significantly decreased in the last months (when comparing those 5-3 months prior to death with those 2-0 months to death). Physical functioning, pain, fatigue, appetite loss and overall QoL showed a progressive decline towards death (those 5-3 months prior to death scored worse than those ≥6 months prior to death, and those 2-0 months prior to death scored worse than those 5-3 months prior to death). Dyspnea, insomnia and constipation only deteriorated from 5-3 to 2-0 months before death, and nausea/vomiting only showed a significant worsening when comparing those ≥6 months prior to death with those 2-0 months prior to death.

From these results, it can be concluded that deterioration of symptoms may already occur before the terminal phase, and tends to accelerate close to death ('terminal drop'). The findings accentuate the significance of early, systematic symptom assessment and management in patients with advanced cancer, and point to the need for further prospective studies to identify those factors that best predict which patients are most at risk of high symptom burden, and/or high functional and QoL impairment.

PART II: End-of-life communication and information provision in people with advanced cancer

Trends in communication about end-of-life topics with cancer patients in general practice in three European countries and differences with respect to patient characteristics

Chapter 4 described a trend analysis on communication about end-of-life topics with cancer patients in general practice in Belgium, the Netherlands and Spain in 2009-2010 (Spain: 2010-2011) and 2013-2014. A representative sample of GPs registered all deceased adult cancer patients in their practice and reported for five end-of-life care topics whether they had been discussed with the patient. Overall, diagnosis was the most commonly discussed end-of-life topic in all three countries. In Belgium, significant increasing trends were found between 2009 and 2014 for communication about the diagnosis, for communication about options for end-of-life care, for GPs' awareness of patients' preferences for medical treatment at the end of life and for GPs' awareness of patients' preferences for a proxy decision-maker. In the Netherlands, significant increasing trends were found for GPs' awareness of patients' preferences for medical treatment and for GPs' awareness of patients' preferences for a proxy decision-maker. In Spain, comparable upward trends for GPs' awareness of patients' preferences for medical treatment and a proxy decision-maker were visible, but did not reach statistical significance. Besides increasing trends, we found unexpected declines over time for two topics. Both in the Netherlands and in Spain, there was a significant decrease in communication about options for end-of-life care and about psychological or social problems. In general terms, the aforementioned trends were seen across patient groups (age, gender, cancer type, place of residence in the last year of life, place of death).

These findings tell us that end-of-life communication in primary care in Europe can change considerably in a relatively short time span. Despite cross-national differences in the prevalence and magnitude of change, overall trends were similar to a substantial degree. Challenges to the continuity of communication between GPs and patients are an important point of attention. Further research should study end-of-life communication and the process advance care planning (ACP) as a whole, throughout the cancer care trajectory, and across healthcare providers of varied specialties and multiple settings.

Information provision by specialist palliative care services and involvement in decision-making: evaluations of people with cancer and bereaved relatives

Chapter 5 explored how cancer patients being supported by specialist palliative care services (PCSs) in Belgium evaluated information provision and involvement in decision-making. Furthermore, we investigated how relatives of cancer patients who had died while under the guidance of specialist PCSs evaluated information provision by these services, and how evaluations varied with respect to the patient's age and gender, length of guidance, and the type of palliative care service. Overall, the majority of patients reported positive experiences of the amount of information they received regarding their illness and end-of-life care, the extent to which their wishes were respected by professional caregivers and the opportunity to participate in decision-making about their care. Bereaved relatives' evaluations were also predominantly positive with respect to the amount of information received on the patient's illness, care and impending death. Information provision seemed to have been most satisfactory to both patients and bereaved relatives in cases where care was provided within a separate hospital-based palliative care unit (PCU) – offering personalized, continuous care – as compared to cases where care was provided by a hospital-based mobile palliative support team or a multidisciplinary mobile palliative homecare team – mainly providing support and advice to other healthcare professionals. We also found that the patient's age influenced evaluations of decision-making. Older people with cancer were more likely to have had a less active role in making decisions about their care and felt that their personal wishes were not always taken into account. Relatives of younger adult patients (18-64 years) more often reported having received less information than they considered necessary about the person's condition and treatment than relatives of older patients (65-84 years).

Our results contribute to existing literature on the benefits of PCSs by showing that these services are well equipped to delivering information and support catered to individual patient and family needs. The findings may help optimize information provision and decision-making in cancer care within the various palliative care structures, and inform other countries in the process of improving their palliative care policies. Future studies will be needed to clarify how services can learn from each other's best practices.

PART III: End-of-life decisions and the preceding decision-making process in people who died from cancer

Prevalence and characteristics of end-of-life decisions in different cancer types

Chapter 6 concentrated on the prevalence of end-of-life decisions with a possible or certain life-shortening effect (ELDs) and characteristics of the underlying decision-making process among people who died from different cancer types in Belgium. A nationwide death certificate study was conducted based on a large random sample of all deaths in Flanders (2013). Treating physicians completed a questionnaire concerning medical decisions made at the end of life and the decision-making process leading to the ELD. In general, the occurrence of ELDs was (equally) high in all cancer types. More than one in ten deaths (10.4%) were from euthanasia or physician-assisted suicide. This relatively high rate of assisted dying was consistently noticeable in all cancer groups (8.7-12.6%). The administration of drugs with the explicit intention to hasten death (life-shortening acts) without the explicit request of the patient occurred in 1.8% (1.0-3.4%). The two reasons most often reported by physicians for the ELD with the most explicit life-shortening intention were physical suffering and a lack of prospect of improvement. After adjustment for confounders, ELDs were shown to be more often based on anticipated further suffering and unbearability of the situation for close relatives in hematological cancers than in other types of cancer. While patients with decision-making capacity were regularly involved in the decision-making process (71.6-92.3%), decision-making still took place without the patient's input in almost 20% of cases. Remarkable was the low rate of written advance directives (less than 6%) and the suboptimal involvement of family members that we found in patients lacking decision-making capacity (ELD was discussed with the family in less than 70% of cases in all cancer groups, except for breast cancer). For those without capacity, neither the presence of a living will nor the decision being discussed with the family could be related to cancer type.

The findings may indicate that universal protocols and training of care practices across oncological settings in Belgium have resulted in a uniform approach to end-of-life care and palliative care. Irrespective of their specific diagnosis, cancer patients seem to have equal opportunities to go through the process for access to assisted dying practices, which are common within cancer care in Belgium. There is room for improvement with regard to (encouraging) the involvement of patients and relatives in decision-making. Policy makers need to develop strategies for the implementation of ACP programs and provide healthcare facilities with the necessary education and resources.

DISCUSSION OF THE MAIN FINDINGS

PART I: Self-reported emotional and physical functioning, symptoms and quality of life in people with advanced cancer

The symptom experience of patients with advanced cancer

Among the two large advanced cancer samples studied in **Chapter 2** and **Chapter 3**, and in line with the literature, fatigue was overall the worst scoring (most severe) self-reported symptom. It is important to note that fatigue felt by advanced cancer patients differs from the 'normal' fatigue of daily life. It has been defined as a 'distressing, persistent, subjective feeling of physical, emotional and/or cognitive tiredness associated with cancer or cancer treatment.' Other important symptoms included dyspnea, pain, insomnia and appetite loss, whereas nausea/vomiting had lower levels of severity in both samples.

Previous work has indicated that cancer patients experience symptoms throughout their illness trajectory towards the end of life, and that the burden is likely to increase as the disease progresses. Our findings confirmed this by showing that some symptoms – dyspnea, insomnia and constipation – as well as outcomes such as emotional functioning seem to remain fairly stable until they deteriorate relatively shortly before death, while other symptoms – pain, fatigue and appetite loss – and outcomes such as physical functioning and overall QoL tend to start declining 'as early as' months before the final phase of life, and deteriorate more rapidly when the time of death comes closer. This is why quality care requires systematic symptom assessment and management throughout the illness trajectory. This could include the routine use of questionnaires which center the patient experience, known as patient-reported outcome measures (PROMs), for systematic detection of problems and needs.

Unfortunately, even though the majority of oncologists believe that earlier engagement with palliative care specialists improves symptom management, health-related communication and continuity of care, referrals to palliative care are often not initiated until late in the course of the illness. One important reason for the underutilization of early palliative care is the negative connotation attached to the label 'palliative care'. Some specialists have called for a rebranding of palliative care to highlight its benefits for people in many different situations, reduce the stigma and make the term more acceptable to all involved.

Different challenges for different countries in Europe: variations in healthcare organization

Our study described in **Chapter 2** revealed similarities as well as significant dissimilarities between six European countries in patient-reported functional status, symptoms and QoL. Disparities between countries in patient outcomes may arise from the fact that health and social cancer care services are organized in different ways in different countries. Almost all European countries have adopted a national cancer plan during the last decade, but each system has its own context and environment, having evolved under the influence of historical aspects, population characteristics, healthcare structures, or past and present government policies. As long as a system performs well, is cost-effective and yields desirable outcomes, it is not necessary to impose identical manners everywhere. In many systems, however, there is room for amendment or improvement. The performance of healthcare services in different countries can be evaluated using a number of indicators. One example of such a performance indicator is the *availability* of different services (e.g., availability of trained palliative care staff; appointment waiting list time; the number of services a patient can choose from). Another example is the *access* to healthcare services (e.g., geographical accessibility; affordability; restrictions due to social and cultural barriers; restrictions or delays due to internal procedures or bottlenecks in the healthcare system). A final, important performance indicator is the *quality* aspect of cancer care, which can be subdivided in three domains: quality of *structure* (material and human sources needed, organizational factors, access to medical technologies, availability of multidisciplinary teams), *process* quality (sum of actions that make up health care, shaped by clinical and policy guidelines, monitored through cancer registries and partly reflected by patient satisfaction) and quality of *outcome* (can be measured by health-related QoL). There has been increasing interest in the use of standardized outcome assessment methods and the measurement of patient-reported outcomes. More steps have also been taken to study and benchmark quality of care across countries, for example by the EU Commission and the Organisation for Economic Cooperation and Development (EOCD).

Different challenges for different countries in Europe: variations in culture

The observed differences between the six countries studied in **Chapter 2** – Belgium, Denmark, Italy, the Netherlands, Slovenia and the UK – in patient-reported functional status, symptoms and QoL might also be (partly) explained by differences in cultures, ethical, religious and political backgrounds. The concept of culture is fundamentally relevant to health care at all levels. It reflects the way people with cancer perceive their illness and/or its treatment and plays a considerable role in communication, interactions with healthcare providers and medical decision-making processes. Health outcomes are also likely to be affected by 'collective health behavior' in the shape of national health care policies.

In our study, the Netherlands and Denmark scored very highly on emotional functioning and QoL scores and had the lowest symptom scores. Of the six countries included, they are perhaps the two that share the most similarities. Both countries have state-sponsored, well-functioning healthcare systems with good accessibility; a Protestant Christian heritage, which generally denotes a more progressive stance to euthanasia than countries with Catholic heritage (such as Belgium and Italy); and consistently rank as some of the top happiest countries in the world according to the World Happiness Report. The high scores in this study could possibly be a natural consequence of the high baseline happiness in these countries. The more widely ranging scores in other countries may reflect their more different backgrounds, but also more localized disparities such as the region or even the specific institution where the study took place. The UK showed generally less favorable results, possibly due to chronic underfunding of the National Health Service and a below average health expenditure on cancer care.

It is most likely that the inter-country variation in our study is caused by a combination of differences in the performance of healthcare services on the one hand and differences in cultural aspects on the other. Within the context of our study, we have not been able to explain which part could have been related to differences in healthcare organization and which part could have been related to culture.

PART II: End-of-life communication and information provision in people with advanced cancer

Discussing diagnosis, options for end-of-life care and psychological or social problems in primary care

The physician-patient relationship has gone through a major transition in the past decades, from the traditional paternalism-based model to a patient-centered approach. A core element of this approach is shared decision-making, and effective shared decision-making requires that patients are appropriately informed about their medical condition. Healthcare providers have a tendency to underestimate patients' information needs and overestimate their illness knowledge and understanding. Although in some cases patients prefer not to have full information about their health condition or serious diagnosis, the vast majority of patients, including cancer patients, want to receive detailed information about their disease and expected outcomes.

While the issue of truth-telling is still handled differently in different countries and cultures, and healthcare providers often remain reluctant to disclose and discuss information concerning the (advanced illness) diagnosis, there has been a growing global trend toward disclosing the truth. Most Western countries today have implemented a legal requirement for doctors to properly and honestly inform patients with regard to their condition. This general trend to tell patients about a serious diagnosis seems to be reflected in the high percentages of communication about diagnosis we found across countries in the current study. We should, however, be cautious not to overreach in drawing conclusions from this information, because it is not clear from our data whether conversations about the diagnosis might or might not have included communication and information about, for example, prognosis.

Do GPs know and address what their patients want?

GPs' position at the heart of the healthcare system and their potential to establish long-term, ongoing relationships with their patients places them in a good position to initiate communication about end-of-life care and to encourage patients and families to talk about their personal needs, values and preferences. According to our results, there appears to be an overall trend over time among GPs to becoming better informed about cancer patients' preferences for medical treatment and a proxy decision-maker at the end of life (**Chapter 4**). These findings seem to reflect GPs' increasing awareness and perhaps recognition of these specific aspects of advance care planning (ACP). If the GP is aware of a patient's choice of a surrogate decision-maker, it will be easier for him/her to reach the assigned relative within a short timeframe to discuss the treatment and care process. Unfortunately, the study conducted did not collect any information on the actual behavior of GPs in relation to their contact with patients – so if it is genuinely true that GPs are increasingly gaining greater awareness of their patients' preferences for treatment and proxy decision-maker at the end of life, it remains unknown so far whether, and how they act upon this knowledge.

Next, one could argue that the observed upwards trends are just following general patterns of enhanced interest in relatively recent concepts such as ACP and patient-centered communication in Europe. Both have been receiving greater policy attention over the past years, and in several countries attempts have been made to realize and implement palliative care education, training and protocols. However, the two items included in our analysis are very specific, representing only a fraction of the total concept of ACP, and cannot be used to make any statements about the entire process.

The importance of effective communication and information sharing between professionals at the primary and secondary healthcare level

Our results showed decreasing trends in communication about options for end-of-life care and psychological or social problems between GPs and patients. The reason for this could lie in the phenomenon of increasing specialization and task differentiation in primary and secondary care. Literature has shown that cancer patients may 'disappear' from the GP's practice into hospitals, where they spend more time under specialist care during and after treatment. This means conversations about options for end-of-life care and about psychological or social problems may have happened increasingly more often with, for instance, specialist cancer nurses in hospitals.

Qualitative research on the position of GPs in continuous primary end-of-life care shows that people who are terminally ill often assign GPs a prominent role in diverse aspects of two forms of continuity. 'Relational continuity' refers to maintaining a continuing relationship with the same GP. Examples are keeping in touch after referral and feeling responsibility towards the patient. 'Informational continuity' refers to utilizing information about the patient, such as the patient history or individual circumstances to deliver tailored, personalized care. Examples are proper exchange of information across GPs, specialists and healthcare facilities. If multiple disciplines from primary and secondary care were involved in the care for a patient, particularly specialist physicians, this can lead to errors and miscommunication, necessitating a more active role from patients and relatives themselves. Some patients also report a lack of coordination, and thus vagueness about one's central contact, which caused them a lot of distress. This highlights the need for frequent communication between GPs and other healthcare providers, even in cases where one particular role (such as the GP) is seen by the patient as the main point of contact and care.

Experiences of Belgian cancer patients and relatives regarding information provision and their involvement in decision-making in specialist palliative care services

As described in **Chapter 5**, a great majority of people with cancer being supported by specialist palliative care services (PCSs) and bereaved relatives of cancer patients who had died while under the care of PCSs appeared to be generally satisfied with information provision, indicating that they had received 'just the right amount' of information about the illness and (end-of-life) care. Patients' involvement in decision-making was also generally positively evaluated. Previous work has suggested that information provision is a commonly reported unmet need among cancer patients and that information about palliative or end-of-life care is often not provided, not even in cases where patients had late-stage illness. In Belgium, the patient's right to be informed – but also the right not to be informed on his/her explicit request – is one of the main principles prescribed by the Act on Patients' Rights which took effect on 22 August 2002. Our research suggests that patients with advanced cancer and their relatives are more likely to have their information needs met in an environment of specialist palliative care, but that not all specialist palliative care services (PCSs) were equally succesful in this. In line with the literature, information provision seemed to have been more satisfactory to both the patients and the bereaved in the case of separate hospital-based unites (PCUs) than in the case of specialist care teams offering support and advice to other healthcare professionals. The structure of hospital-based PCUs appears most effective in facilitating a supportive environment for optimal information provision, probably because the patient and/or family members are addressed in a more *tailored* and *direct* way.

Shared decision-making in cancer care: are older people being heard?

Ageism – stereotyping, prejudice and discrimination against people on the grounds of their age – is a global concern, highly common across countries, that will likely increase even more with population ageing. It may be reflected in clinical practice and decision-making processes, and can significantly impact people's health and wellbeing. In general, older patients are less likely to be actively involved in medical decision-making than younger patients, and less likely to have their personal care wishes taken into account, as was also seen in our study (**Chapter 5**). Physicians' assumption that older cancer patients desire less information and wish to leave decisions to their healthcare providers has been shown to be an important barrier to older patients' participation in shared decision-making. Healthcare providers are inclined to address the younger relatives of older patients, thereby bypassing the patient. Often, they are unaware of discriminatory tendencies in their communication routines, or just presume that younger family members are faster when it comes to hearing and understanding information. This could lead to inequity in the quantity and quality of care provided to older patients and, consequently, in their health outcomes. Active participation has been associated with positive health outcomes such as better overall QoL and higher physical and social functioning. People who actively participate in decision-making are usually more informed, better able to assess risks and benefits, and less likely to experience decisional conflict and dissatisfaction.

It should be noted that based on the literature, older patients tend to prefer a less active role in medical decision-making, whereas younger patients generally prefer greater involvement or a shared role. 'Pushing' patients to be an active participant in medical decision-making if they do not want to be in this position can have adverse consequences such as decisional regret, increased anxiety, a lack of confidence in decision-making and stress. However, a lower participation preference might also arise from a fear of not being competent enough to make a sensible contribution to the discussion and/or slowing down the conversation. This may be particularly relevant in cases where patients have limited health literacy, which is more common among the elderly. Physicians will need to spend more time communicating with older cancer patients to help them understand their choices and preferred level of involvement in decision-making, and to be able to respect and respond to their unique goals, values and preferences – the cornerstone of patient-centered care.

PART III: End-of-life decisions and the preceding decision-making process in people who died from cancer

Suboptimal involvement of cancer patients and families in decision-making towards the end of life in Belgium

In cases of terminal illness, patients, relatives and healthcare practitioners may find themselves confronted with a number of complex, sensitive decisions that should be made regarding treatment and care near the end of life. This includes end-of-life decisions (ELDs) that have the potential to hasten the patient's death, either implicitly (when death is an anticipated, yet unintended consequence of the medical decision), or – less commonly – explicitly (when death is the intended outcome of the decision). Our findings revealed that in approximately 20% of cases where the patient was judged competent at the time, they were nevertheless not involved in the decision-making process preceding the ELD. Although this shows improvement over time compared to previous studies, it still seems suboptimal. One possible explanation may lie in the fact that conversations about the end of life are still often seen as demanding and stressful for both the physician and the patient. Physicians may feel uncomfortable talking with patients about the stigmatized subject of death or dying; lack experience with such conversations; or the tools, guidelines and training around end-of-life communication available to them may be inadequate. Another possibility might be that certain ELDs, notably 'intensifying alleviation of pain and symptoms', have become such common practice in cancer care, that physicians may not always feel the need to discuss them. Nonetheless, conforming to the principle of patient autonomy, all possibly life-shortening practices must be discussed with the patient, unless he or she has specifically expressed otherwise. The findings of this dissertation underscore the importance for physicians and other healthcare providers to keep encouraging patients to be active participants in the process of decision-making, bearing in mind patient's individual preferences for the degree of participation in treatment decisions near the end of life.

While respecting the patient's wishes is paramount in decision-making, the patient's relatives can make important contributions to decision-making too. Palliative care should aim to improve the quality of life of *both patients and their relatives* who are confronted with life-threatening illness. Therefore, involving relatives and other important people close to the dying patient in decision-making is regarded as good medical practice for physicians and other healthcare professionals. The involvement of family members in decision-making becomes even more important when the patient becomes incompetent. Our findings showed that where the patient was lacking in competence, relatives were involved in the decision-making process in less than 70% of cases (in all cancer types, except for breast cancer where this percentage was slightly higher). Given that prior research has shown that the vast majority of cancer patients want their families involved in medical decisions near the end of life, specifically in case of loss of competence our study's results indicate that there is still room for improvement.

High occurrence of euthanasia or physician-assisted suicide in advanced cancer in Belgium

Our results showed that the occurrence rate of ELDs was equally high in the five most common cancers (gastrointestinal, respiratory, genitourinary, breast, hematological). More than one in ten cancer deaths (10.4%) registered in 2013 were from euthanasia or physician-assisted suicide. This is an important rise if we compare this percentage with the 5.6% of all cancer deaths due to euthanasia registered in 2007. The findings led us to conclude that assisted dying practices are widespread within cancer care in Belgium. In general, cancer patients appear to have equal opportunities to access and go through the procedures of euthanasia, regardless of their specific cancer diagnosis. On a societal level, this is an indication that assisted dying is fairly well imbedded in care at the end of life of cancer patients. Of course, end-of-life decisions are strongly related to the healthcare system and the regulating framework within a country. Belgium was the second country in Europe to legalize euthanasia in 2002, in specific circumstances and subject to statutory safeguards. The seemingly broad integration of euthanasia in end-of-life care for cancer patients in Belgium may have been a consequence of the training and clinical support of medical professionals by the 'Life End Information Forum' (LEIF) physicians, but also of the continuous debate about euthanasia in the media since legalization, which can have led to increased awareness of the rights of the terminally ill and to an increase in the acceptance of euthanasia.

However, it is important to note that there is little evidence on how well euthanasia is integrated in palliative care in Belgium. Moreover, the relationship between euthanasia and palliative care can go both ways. Good palliative care could possibly reduce the numbers of requests by patients due to proper symptom control leading to less suffering, but it could also lead to an increased request for euthanasia by terminally ill patients due to increased communication and the creation of a safe environment.

The relevance of this dissertation in light of recent advances in cancer therapeutics

For four out of five studies (**Chapter 3-6**) presented and discussed in this dissertation, data collection occurred more than five years ago. Significant progress has been made in cancer therapy over the past decade. Immune-based therapies have already shown successful in the treatment of many cancers, and can – alone or in combination with conventional treatments – prolong life in people with advanced-stage cancer. This does not diminish the importance of (timely) palliative care involvement, which should be based on what patients *need*, independent of prognosis or treatment intention. People who are surviving with incurable cancer for long periods of time may show great variations in their need for palliative care. Research has shown that patients may experience physical, emotional and existential distress during the life-prolonging phase of treatment. Thus, regardless of the recent developments, optimizing QoL and relieving suffering remain primary goals of treatment.

The WHO also formulates palliative care as an approach in which oncology care and palliative care are integrated or given in parallel. ‘*... It is applicable early in the course of the disease, in conjunction with other therapies that are intended to prolong life.*’ Palliative care needs should be assessed as an ongoing process *from diagnosis onwards*. When cancer treatment and palliative care are provided simultaneously, patients benefit from the expertise of both oncology and palliative care teams – extra important in this era of novel cancer therapeutics, given that immune-based therapies are less toxic and therefore more suitable for people closer to the end of life than standard treatments. When treatment is aimed at cure or prolonging life, most care throughout the illness trajectory can be provided at the generalist level by healthcare professionals with basic competence in palliative care – in this context mainly oncologists. With cancer having more and more a chronic character, generalist primary care providers (GPs, community nurses) are also increasingly being recognized as having a central position in cancer control. If symptoms become very difficult to manage, generalist caregivers will seek advice from, or refer to specialist palliative care services.

IMPLICATIONS AND RECOMMENDATIONS

Challenges and directions for future research

1) Investigate in depth the reasons for cross-country variation in important patient-reported outcomes in cancer

Healthcare professionals and policy makers in cancer care share the same critical goal: assuring that people with cancer who need healthcare services receive the best possible care, in the right place and at the right time, sensitive to their needs and preferences. Nonetheless, improving quality of cancer care has proven to be a serious challenge for many nations, and substantial differences in care outcomes persist across countries. Our results underlined this, as we found some clear variations in patient-reported functional status, symptom severity and QoL across patients living in different countries. There are numerous factors that could possibly contribute to these findings. For instance, differences may reflect heterogeneity in national health systems and healthcare organization across countries; differences in cultural practices and attitudes; and differences in the education, financing and national cultures of palliative care. The design of the present study did not allow for drawing firm conclusions about underlying systemic reasons. Since a better understanding of these reasons and explanations might guide eventual courses of action, we believe that this is an essential area of further research.

2) Conduct longitudinal research to identify those factors that predict important patient-reported outcomes and their evolvement over time

Due to the advances in cancer therapy over the past few decades, more and more people are surviving for an extended time course with cancers that are considered incurable. During their cancer journey, these individuals have to deal with difficult continuing challenges in setting and shifting personal goals and in planning their care to achieve these goals. This is why longitudinal research designs involving prolonged time frames and large amounts of data are so important: they allow us to recognize and determine certain patters that shorter term research does not. Our research on the course of emotional functioning, physical functioning and symptom intensity over time in palliative care cancer patients was explorative in nature and did not specifically investigate factors associated with the evolution of these patient outcomes over time. We could therefore not determine what could characterize patients with different levels of functional impairment, symptomatology and QoL throughout the course of the illness towards death. This highlights the need for further prospective studies to identify those factors that predict which patients are most of risk of high symptom burden, and that can be targeted to prevent poor patient outcomes.

3) Study advance care planning among cancer patients and different healthcare professionals throughout the illness trajectory

Patient-centered communication and advance care planning (ACP) have received increasing policy attention in Europe over the last years. In this dissertation, we looked at trends in the prevalence of GP-patient conversations about certain end-of-life topics. However, our study only reported if topics were discussed according to the GP, and this does not represent the full complexity of end-of-life communication with cancer patients. Due to the ongoing increase in the specialization of cancer care and palliative care, it may be that certain topics are more often discussed with palliative caregivers rather than with GPs. Future research should provide a more complete picture by incorporating the ACP process as a whole throughout the entire illness trajectory, and by including the perspectives of patients and their families, as well as the various involved healthcare providers at all healthcare levels.

Implications and recommendations for clinical practice and policy

1) Incorporate routine assessment of patient-reported outcomes into clinical practice as standard part of cancer care throughout the illness trajectory

Our findings confirm that the optimization of symptom control, functional status and QoL remains a challenge to healthcare workers in palliative cancer care across European countries, and that this becomes even more difficult in later stages of the disease trajectory, as the illness progresses towards the end of life. We strongly emphasize the importance of including periodic subjective, patient-reported outcomes assessments as part of healthcare providers' routine ways of working in cancer care.

Patient-reported outcome measures (PROMs) are increasingly used in clinical settings for tracking symptoms, needs and progress of individual patients over the course of care and have a range of benefits. Unfortunately, they are rarely embedded as part of routine oncological care. Advances in technology have resulted in the development of electronic systems to facilitate the collection and reporting of patient-reported outcomes across settings. Electronic PROMs allow for immediate display of interpretable results to the clinician and easier storage, linkage and transfer of patient results, which facilitates communication and information transmission during consultations.

2) Facilitate strong, collaborative relationships among different professions across care settings in order to support information sharing and continuity of care

Palliative care has a multidisciplinary nature by definition. Consequently, collaboration and coordination of palliative care can be complex. It involves numerous disciplines and transitions between different locations and levels of care throughout the disease trajectory. This may lead to breaks in continuity of care and information. In order to preserve an effective doctor-patient relationship and ensure continuity of care, GPs should be more proactive in maintaining contact with their patients after diagnosis. At the same time, specialist carers should take responsibility for keeping GPs informed of their patients' care. Collaboration could be further facilitated by use of electronic health records, which will likely improve GPs' access to patient information and enhance information transfer among the generalist and specialist care setting. The support provided in the PCU setting, which is scored highly by both patients and relatives, could be used as a performance 'benchmark' by other specialist services. In order to improve care and to make it possible for professions to learn from each other's best practices, creating and nurturing optimal cooperation and collaboration between healthcare providers is an important area of attention for policy makers.

3) Invest in education and training for future and current health workers in palliative cancer care to promote interprofessional collaboration

The previous recommendation highlighted the need for strong, collaborative relationships among healthcare providers from different care settings as a key factor for sustaining continuity of care in cancer care throughout active treatment, supportive care, palliative care, survivorship or end-of-life care. Interprofessional collaboration is a fundamental competence that needs to be strongly supported at policy level, and this calls for increased educational efforts. To improve cancer care throughout the full care trajectory on a larger scale, interprofessional cooperation needs to be given more attention and should be sufficiently integrated into the curricula of all basic (e.g., medical school, nursing school, social work) and specialized, post-graduate education (e.g., for GPs, oncologists, palliative care physicians, oncology nurses).

4) Implement strategies to improve the engagement of patients and family in end-of-life decisions that may hasten the patient's death

Patient involvement in medical decision-making is considered a crucial component of patient-centered care and becomes even more vital when a patient approaches the end of life. The majority of cancer patients want to be involved in decisions about end-of-life care. However, our findings showed that according to their physicians, 20% of competent cancer patients were not involved in the decision-making process preceding end-of-life decisions (ELDs). Likewise, less than 70% of relatives were involved in the decision-making process in cases where the patient was deemed incompetent, although it is known from earlier work that most people with cancer prefer their family members to take part in medical decision-making near the end of life, especially when the patient lacks decision-making capacity.

There are several barriers for healthcare professionals to actively engaging patients and their families in end-of-life decision-making, such as professional caregivers' or patients' resistance to doing so, not having enough opportunity or time to talk to those people, a lack of training received by healthcare professionals, a lack of understanding of the important role of relatives, not being aware of who to talk to, or not being able to get in touch with the right people quickly enough in an urgent situation. The assignment of a central family caregiver who has a direct line of communication with the patient's physician to discuss care and treatment, if necessary, should be part of standard cancer care. Emergency contact details and back up contact details must be on file from early on in the disease trajectory and need to be accessible to multiple caregivers.

For policy makers it would be useful to carefully monitor the evolution of patient and family involvement in end-of-life care and ELDs over time. Possible changes over time would inform healthcare providers and healthcare managers whether they need to take action, for example by enhancing education and processes, in hospital settings as well as outside the hospital setting.

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Nederlandstalige samenvatting

INTRODUCTIE

Achtergrond

Veranderingen in (opvattingen over) het sterven

De stervenservaring en de manier waarop mensen omgaan met de dood en met sterven zijn niet altijd hetzelfde geweest. Een eeuw geleden kwam het overlijden vaak abrupt en voornamelijk als gevolg van infecties, ongevallen of complicaties bij bevallingen. Dankzij de verbetering van de volksgezondheid, medische kennis en technologie in de loop van de voorbije eeuw – en dientengevolge een stijgende levensverwachting en een toenemend aantal ouderen – is het aantal sterfgevallen met acute oorzaken gedaald en geleidelijk vervangen door een stijgend aantal overlijdens ten gevolge van zogenaamde 'niet-overdraagbare' ziekten, met als grootste twee hart- en vaatziekten (wereldwijd naar schatting 19,7 miljoen sterfgevallen per jaar) en kanker (wereldwijd naar schatting 9,6 miljoen sterfgevallen per jaar). Deze ziekten hebben over het algemeen een langduriger ziekteverloop, met een functionele achteruitgang van maanden of jaren.

Veranderingen in perspectieven op de zorg voor stervenden

De moderne hospicebeweging, opgericht in de jaren 60 door verpleegkundige en arts Dame Cicely Saunders (1918-2005) was een belangrijk markeringspunt in de zorg voor stervenden en ongeneeslijk zieken. Deze beweging legde de basis voor, en ontwikkelde zich verder tot het hedendaagse concept van palliatieve zorg. In de jaren 70 werd palliatieve zorg synoniem voor fysieke, psychosociale en spirituele ondersteuning van patiënten met een levensbeperkende ziekte, verstrekt door een multidisciplinair team. Palliatieve zorg richt zich op het behoud van comfort en kwaliteit van leven voor mensen die gedurende langere tijd met meervoudige, complexe problemen te maken hebben. Palliatieve zorg ondersteunt het behoud van een gevoel van waardigheid en controle over iemands levensomstandigheden, met name in de latere fasen van een invaliderende, progressieve ziekte.

Palliatieve zorg en zorg rond het levenseinde bij mensen met gevorderde kanker

Groeiende populatie van mensen met kanker in een gevorderd stadium

De incidentie en het sterftecijfer van kanker nemen wereldwijd snel toe als gevolg van een groeiende en vergrijzende bevolking en een veranderde prevalentie en verdeling van bepaalde risicofactoren voor kanker, zoals voeding en een gebrek aan lichaamsbeweging. Hoewel kanker in een gevorderd stadium meestal niet kan worden genezen, kunnen behandelingen helpen de voortgang te vertragen en het leven van mensen voor maanden of zelfs jaren te verlengen. De stijgende incidentie van kanker en de langere overlevingsduur van patiënten met kanker in een gevorderd stadium leggen wereldwijd een toenemende druk op de bevolking en gezondheidszorgstelsels en gaan op het gebied van volksgezondheid gepaard met een sterk groeiende behoefte aan kwalitatief hoogwaardige palliatieve zorg en zorg rond het levenseinde.

Palliatieve zorg

Palliatieve zorg gaat uit van het principe dat elke patiënt zijn of haar eigen verhaal, relaties en culturele achtergrond heeft, en dat hij/zij respect verdient als individu. Dit respect houdt onder andere in dat de beste beschikbare medische zorg wordt geboden, zodat men een zo volwaardig en comfortabel mogelijk leven kan leiden. Een van de meest gebruikte en geciteerde definities van palliatieve zorg werd in 2002 geformuleerd door de Wereldgezondheidszorgorganisatie (WHO): 'Palliatieve zorg is een benadering die de kwaliteit van het leven verbetert van patiënten en hun naasten die te maken hebben met een levensbedreigende aandoening, door het voorkomen en verlichten van lijden, door middel van vroegtijdige signalering en zorgvuldige beoordeling en behandeling van problemen van fysieke, psychische, sociale en spirituele aard.' Aanvullend benoemt de WHO enkele grondbeginselen. Palliatieve zorg legt de nadruk op de verlichting van pijn en andere problematische symptomen. Het leven wordt bekrachtigd, de dood beschouwd als een normaal en natuurlijk proces dat niet vertraagd of versneld wordt. Er wordt gebruik gemaakt van een teambenadering om tegemoet te komen aan de behoeften van patiënten en hun naasten, indien geïndiceerd met inbegrip van rouwbegeleiding. Palliatieve zorg kan een positief effect hebben op zowel de kwaliteit van leven als het ziektebeloop.

Historisch gezien is palliatieve zorg ontstaan binnen de oncologie, als zorg voor kankerpatiënten bij wie het levenseinde nadert. Vandaag de dag zijn kankerpatiënten in veel landen nog altijd de grootste groep patiënten die palliatieve zorg ontvangen. Hoewel de focus oorspronkelijk lag op terminale kankerpatiënten voor wie alle actieve behandelingen beëindigd waren, wordt nu algemeen erkend in onderzoek, praktijk en beleid dat palliatieve zorg zich niet beperkt tot terminale ziekte. Tegenwoordig wordt een 'traject'-model van palliatieve zorg gehanteerd, dat curatieve of levensverlengende therapie en palliatieve zorg integreert. Palliatieve zorg wordt geïntroduceerd wanneer een levensbeperkende ziekte, zoals kanker, wordt gediagnosticeerd, en gaat een steeds prominentere rol spelen naarmate de ziekte vordert, inspelend op de individuele behoeften en voorkeuren van de patiënt. De aanvankelijke focus op curatieve behandeling neemt geleidelijk af en verschuift naar een nadruk op verlichting van symptomen en psychosociale ondersteuning van patiënten en hun zorgverleners.

Zorg rond het levenseinde

De termen 'palliatief' en 'palliatie' worden vaak vereenzelvigd met het verlenen van zorg aan het einde van het leven. Palliatieve zorg en levenseindezorg zijn echter geen identieke begrippen, hoewel ze elkaar gedeeltelijk overlappen. Palliatieve zorg omvat zorg rond het levenseinde, maar daarnaast ook veel méér dan dat, vanaf het moment van de diagnose tot aan het overlijden. Levenseindezorg verwijst in nauwere zin naar zorg die wordt verleend in de laatste fase van het leven van een patiënt, over het algemeen in de laatste paar maanden. De duur van de periode rond het levenseinde hangt sterk af van de onderliggende diagnose en het klinisch beloop, en is uiteraard in veel gevallen moeilijk te voorspellen. In de context van dit proefschrift hebben we gekozen voor een pragmatische definitie van levenseindezorg, verwijzend naar alle zorg gericht op de behandeling en ondersteuning van mensen met kanker in een gevorderd stadium die het einde van hun leven naderen, ongeacht of de ontvangen zorg palliatief of levensverlengend van aard is.

Zorgaanbieders op het vlak van palliatieve zorg en zorg rond het levenseinde: generalistische en gespecialiseerde palliatieve zorg

Ongeacht de zorgsetting kan palliatieve zorg worden verleend door het toepassen van vaardigheden op generalistisch en specialistisch niveau. Ofschoon palliatieve zorg niet zelden ten onrechte wordt gezien als uitsluitend verwijzend specialistische zorg, heeft niet iedere persoon een specialist nodig om de juiste zorg te ontvangen. De meeste zorg voor mensen met een levensbedreigende aandoening of mensen die het einde van hun leven naderen vindt dan ook plaats in een eerstelijnszorgsetting. Het toepassen van een passende combinatie van generalistische en gespecialiseerde zorg is een meer duurzame en kosteneffectieve oplossing voor optimale dekking van de populatie met palliatieve zorgnoden, dan het leveren van gespecialiseerde zorg in alle mogelijke situaties.

Generalistische zorg wordt meestal verleend door reguliere zorgverleners die al enige klinische ervaring hebben en een basisopleiding hebben genoten in de palliatieve zorg, maar die zich niet primair identificeren als palliatieve zorgverlener. In veel landen zijn huisartsen de belangrijkste aanbieders van generalistische palliatieve zorg. Andere voorbeelden van generalistische palliatieve zorgverleners zijn oncologen, verplegend personeel en maatschappelijk werkers. In zeer uitdagende of complexe omstandigheden zullen deze zorgverleners specialistisch advies inwinnen of doorverwijzen naar gespecialiseerde palliatieve zorgdiensten.

Zorgverleners gespecialiseerd in palliatieve zorg zijn professionals wier voornaamste verantwoordelijkheid bestaat uit het verlenen van palliatieve zorg. Zij hebben specialistische kennis en competenties verworven en een speciale formele opleiding genoten om de doelstellingen van palliatieve zorg te kunnen dienen. De specifieke rollen en taken verschillen per land, maar in de meeste landen wordt gespecialiseerde palliatieve zorg verleend door een multidisciplinair team dat is toegewijd aan palliatieve zorg en zorg rond het levenseinde. Wanneer een dergelijk team betrokken is blijven patiënten meestal doorlopend zorg ontvangen van hun hoofdarts of klinisch team, hoewel een patiënt in bijzonder veeleisende gevallen kan worden doorverwezen naar een gespecialiseerd team voor continue zorg. Uit eerder onderzoek is gebleken dat patiënten met kanker meer geneigd zijn om gebruik te maken van gespecialiseerde palliatieve zorg en tevens eerder worden doorverwezen naar gespecialiseerde palliatieve zorg dan patiënten met andere aandoeningen.

Palliatieve zorg in de medische oncologie

In haar *position paper* over ondersteunende en palliatieve zorg benadrukt de European Society for Medical Oncology (ESMO) Supportive Care Faculty dat het multidisciplinaire team dat zorgdraagt voor patiënten er actief op moet toezien dat patiënten hun noden kenbaar kunnen maken, die afhankelijk van het ziektestadium kunnen variëren en vaak evolueren in de loop van de tijd. ESMO stelt dat 'meer en beter wetenschappelijk bewijs [...] nodig is, zodat doeltreffende interventies aan kankerpatiënten in *elk* stadium van hun ziekte kunnen worden aangeboden.'

Het *white paper* van de European Association for Palliative Care (EAPC) onderstreept ook het verstrekken van passende informatie over de ziekte, de behandeling en zorgmogelijkheden; ondersteuning bij individuele zorgplanning en besluitvorming; goede communicatieve vaardigheden; prioriteiten/dimensies van kwaliteit van leven (die kunnen veranderen naarmate de ziekte vordert); en een multidisciplinaire aanpak als zijnde algemene en essentiële hoofdthema's van palliatieve zorg.

In de Verenigde Staten werkten de American Society of Clinical Oncology (ASCO) en de American Academy of Hospice and Palliative Medicine (AAHMP) samen om tot een consensusdefinitie te komen van kwalitatief hoogwaardige eerstelijns palliatieve zorg in de medische oncologie. Symptoomevaluatie en -management, communicatie, voorafgaande zorgplanning en zorg rond het levenseinde werden erkend als de belangrijkste domeinen van palliatieve zorg.

Het Lancet Oncology *Commission paper* 2018 geeft een aantal aanbevelingen van een grote internationale commissie van deskundigen over hoe de integratie van oncologie en palliatieve zorg kan worden versterkt. Het paper betoogt dat routinematige evaluatie van symptomen, het gebruik van patiënt-gerapporteerde uitkomsten (PRO-data) en actieve patiëntenparticipatie in de besluitvorming over kankerzorg bijdragen aan een verbeterde symptoombestrijding, betere fysieke gezondheid, beter geestelijk welzijn, en verbeterd gebruik van resources in de gezondheidszorg. Belangrijke hinderpalen voor een doeltreffende integratie zijn het gebrek aan internationale overeenstemming over de inhoud en normen van integratie, onderwijs en onderzoek naar palliatieve zorg in de oncologie. De Commissie roept op tot een heroverweging en reorganisatie van de verstrekking van kanker- en palliatieve zorg, om samenwerking op verschillende zorgniveaus te bevorderen en behandeling te versterken. Dit geïntegreerde model moet tot uitdrukking komen in nationale en internationale plannen voor kankerzorg.

Bovenstaande voorbeelden illustreren dat symptoombestrijding en communicatie tussen patiënt en arts nog steeds worden beschouwd als fundamentele vaardigheden die zorgverleners nodig hebben om patiënten met gevorderde kanker zo goed en zo volledig mogelijk te helpen een zo goed en volwaardig mogelijk leven te leiden, en die centraal staan bij de succesvolle ontwikkeling en implementatie van strategieën voor geïntegreerde palliatieve zorg.

Symptoomlast en kwaliteit van leven

Kanker-gerelateerde symptomen

Mensen met kanker in een gevorderd stadium hebben vaak te kampen met zeer hinderlijke symptomen die het gevolg kunnen zijn van de ziekte zelf en het verloop hiervan, en/of van de kankerbehandeling. In de loop van de tijd kunnen deze symptomen verergeren en het dagelijks leven (meer) gaan belemmeren. Gevorderde kanker heeft tevens een grote impact op de mentale gezondheid, waarbij veel patiënten lijden onder de emotionele gevolgen van hun ziekte, bijvoorbeeld in de vorm van angst en depressieve klachten. Kanker-gerelateerde symptomen en kwaliteit van leven behoren – en moeten ook blijven behoren – tot de hoogste prioriteiten van oncologisch clinici en onderzoekers, maar het feit dat zowel lichamelijke als psychische kanker-gerelateerde symptomen nog zo veelvuldig voorkomen, wijst erop dat deze symptomen niet altijd doeltreffend worden bestreden.

Kwaliteit van leven

Verhoging van de totale overleving is gedurende lange tijd het voornaamste aandachtspunt geweest bij de behandeling van kanker; echter wordt nu algemeen erkend dat behoud van kwaliteit van leven (KvL) een zeer belangrijk uitgangspunt en doel is voor patiënten met vergevorderde kanker. KvL is door de Wereldgezondheidszorgorganisatie (WHO) gedefinieerd als 'de perceptie van personen van hun plaats in het leven binnen de context van de cultuur en waardesystemen waarin zij leven en in relatie tot hun doelen, verwachtingen, standaarden en zorgen [...] die op complexe wijze worden beïnvloed door de lichamelijke gezondheid, psychische toestand, persoonlijke overtuigingen, sociale relaties en zijn/haar relatie tot opvallende kenmerken van zijn omgeving.' Het monitoren van kanker-gerelateerde symptomen en KvL is van cruciaal belang om zorgverleners in staat te stellen beter in te spelen op de veranderende noden van patiënten.

Symptoomlast en kwaliteit van leven in verschillende landen en in de loop van de tijd: nood aan verder onderzoek

Het behouden of verbeteren van de KvL van patiënten en het verlichten van belastende symptomen zijn cruciale uitkomsten van palliatieve zorg. Adequate monitoring van deze uitkomsten is noodzakelijk en kan als leidraad dienen voor patiëntgerichte zorg. Om een beter inzicht te krijgen in de symptoomlast en de KvL bij patiënten met kanker in een gevorderd stadium en om effectievere symptoombehandeling te kunnen realiseren, is er behoefte aan meer kennis over de beleving van symptomen vanuit het perspectief van de patiënt. Aangezien contextuele factoren zoals culturele, ethische en juridische context en aspecten van gezondheidszorgsystemen per land verschillen, zou het waardevol kunnen zijn om cross-nationale verschillen in symptoomlast en KvL te bestuderen om een betere kennis te krijgen van de manier waarop mensen met gevorderde kanker zorg ontvangen in Europese landen en om na te gaan op welke gebieden verbetering mogelijk is. Omdat goede palliatieve zorg een optimale symptoomcontrole en -ondersteuning vereist op *elk* punt van het verloop van de ziekte in vergevorderd stadium en naar het levenseinde toe, is het bovendien belangrijk de functionele status, de symptoomlast en de KvL niet enkel cross-sectioneel, maar ook over een langere periode te evalueren.

Communicatie en informatievoorziening aan het levenseinde

Patiëntgerichte communicatie en het bespreken van onderwerpen rond het levenseinde

Goede, kwalitatieve palliatieve zorg vereist dat artsen zich actief bezighouden met patiëntgerichte communicatie. Dit houdt in dat de patiënt als individu wordt gerespecteerd, dat patiënten worden doorverwezen naar de zorg die zij nodig hebben wanneer dat aangewezen is, dat tijdig adequate en begrijpelijke informatie wordt verstrekt, dat betrokkenheid bij besluitvorming wordt ondersteund en dat beslissingen worden genomen in overeenstemming met de waarden van de patiënt. Er zijn veel voordelen verbonden aan effectieve communicatie, zoals een beter begrip van de ziekte, de zorg- en behandelingsopties, therapietrouw en tevredenheid over de zorg aan het levenseinde. Toch bestaan er verschillende barrières in de communicatie met patiënten en hun naasten, waaronder een algemene terughoudendheid om over de dood of sterven te spreken, of een gebrek aan kennis en opleiding op dit gebied. In de afgelopen decennia is steeds weer gebleken dat diensten in de kankerzorg er niet altijd in slagen te voorzien in de noden van patiënten ten aanzien van communicatie, informatie en ondersteuning. Gebrekkige communicatie kan aanzienlijke gevolgen hebben, zoals ongunstige uitkomsten op het vlak van mentale gezondheid, een verergering van de symptomen en 'agressievere' zorg die ongewenst is c.q. leidt tot verlenging van het lijden. Er is weinig vergelijkbaar, empirisch bewijs betreffende de inhoud en frequentie van communicatie over zorg aan het levenseinde met mensen met kanker in Europa. Contextuele omstandigheden zoals cultuur, de organisatie van het gezondheidzorgsysteem, beschikbare middelen of attitudes ten opzichte van het levenseinde kunnen dergelijke prakijken beïnvloeden.

Informatievoorziening en gedeelde besluitvorming

Het begeleiden van mensen bij het maken van geïnformeerde keuzes over hun eigen zorg en het verlenen van zorg die aansluit bij de voorkeuren van een persoon, zijn reeds vanaf het begin kernwaarden geweest van de palliatieve zorg. Om actief deel te kunnen nemen aan hun zorg, dienen patiënten en hun naasten een adequaat begrip te hebben van de ziekte, behandelings- en zorgopties. Hoewel er altijd rekening moet worden gehouden met persoonlijke waarden, voorkeuren en mogelijkheden bij het afstemmen van (de hoeveelheid) informatie op patiënten en bij het betrekken van mensen bij besluitvorming over de zorg, geeft tegenwoordig een ruime meerderheid van de kankerpatiënten aan dat ze gedetailleerde informatie willen ontvangen over hun aandoening, en wil ongeveer twee derde actief betrokken worden bij de besluitvorming over hun zorg. Ook het verstrekken van informatie aan familieleden of andere naasten speelt een belangrijke rol, aangezien naasten in veel gevallen betrokken zijn bij medische besluitvorming en de voornaamste gesprekspartners kunnen worden van gezondheidszorg- en palliatieve zorg professionals wanneer een patiënt hiertoe zelf niet meer in staat is. Met hun specifieke opleiding in het ondersteunen van patiënten in de laatste levensfase, zou verwacht kunnen worden dat specialisten in de palliatieve zorg veel aandacht besteden aan het optimaliseren van de informatievoorziening aan hun patiënten, en dat diegenen die begeleid worden door palliatieve zorg specialisten de mogelijkheid krijgen om actief betrokken te zijn bij de besluitvorming. Voor zover ons bekend, is er tot nu toe nog geen onderzoek gedaan naar de informatievoorziening – ook met betrekking tot zorg rond het levenseinde – aan kankerpatiënten en hun naasten door verschillende soorten specialistische palliatieve zorgdiensten.

Besluitvorming rond het levenseinde

Potentieel levensverkortende beslissingen aan het einde van het leven

Wanneer het overlijden van een patiënt nadert, moeten de doelstellingen van de medische zorg worden bijgesteld. Het comfort van de patiënt komt dan meer dan ooit centraal te staan bij alle beslissingen die genomen worden over behandeling en zorg. Inspanningen gericht op het verbeteren van het comfort van de patiënt kunnen, zij het zelden, leiden tot een (mogelijke) bespoediging van de dood, meestal als een voorzien maar onbedoeld gevolg van het staken of nalaten van een potentieel levensverlengende maar belastende ingrepen, of om medicatie in hoge dosering toe te dienen om ernstige pijn te verlichten. In sommige gevallen kan bespoediging van het overlijden wenselijk of zelfs een uitdrukkelijk beoogd resultaat zijn, wanneer de patiënt ondraaglijk lijdt en er geen vooruitzicht is op verbetering. Eerder onderzoek heeft aangetoond dat beslissingen rond het levenseinde met mogelijk of zeker levensverkortend effect vaker voorkomen bij kankerpatiënten dan bij niet-kankerpatiënten, mogelijk als gevolg van een hogere symptoomlast bij kanker en de betere beschikbaarheid of toegankelijkheid van palliatieve zorgdiensten. Levenseindebeslissingen bij kankerpatiënten zijn in verschillende studies beschreven, maar voor zover ons bekend heeft geen enkele studie de prevalentie van levenseindebeslissingen en kenmerken van het besluitvormingsproces bij verschillende kankertypes onderzocht. Uit eerdere studies is bekend dat patiënten met verschillende typen kanker niet altijd dezelfde soort en intensiteit van zorg ontvangen aan het levenseinde. Indien een dergelijke variatie tussen kankertypes ook bestaat met betrekking tot de prevalentie van levenseindebeslissingen en aspecten van het besluitvormingsproces, zou dit een aanwijzing kunnen zijn voor een vorm van ongelijkheid in de verstrekking van levenseindezorg aan mensen met gevorderde kanker.

DOELSTELLINGEN VAN DIT DOCTORAAT

Drie doelstellingen, elk met specifieke onderzoeksvragen, vormen de leidraad voor dit doctoraat.

De ***eerste doelstelling*** (**DEEL I**) is het evalueren van zelf-gerapporteerd emotioneel en fysiek functioneren, symptomen en kwaliteit van leven bij mensen met gevorderde kanker. De onderzoeksvragen zijn:

1. Wat is het patiënt-gerapporteerde emotionele en fysieke functioneren, de symptoomintensiteit symptomen en de algehele kwaliteit van leven bij mensen met gevorderde kanker in zes Europese landen, en zijn er verschillen tussen landen? (**Hoofdstuk 2**)
2. Hoe verschillen het patiënt-gerapporteerde emotionele en fysieke functioneren, de symptoomintensiteit en de kwaliteit van leven tussen kankerpatiënten die palliatieve zorg ontvangen in Europa, en hoe ontwikkelen deze uitkomsten zich in de loop van de tijd? (**Hoofdstuk 3**)

De ***tweede doelstelling*** (**DEEL II**) is het evalueren van zelf-gerapporteerd emotioneel en fysiek functioneren, symptomen en kwaliteit van leven bij mensen met gevorderde kanker. De onderzoeksvragen zijn:

3. Zijn er trends in de tijd in communicatie over onderwerpen rond het levenseinde met kankerpatiënten in de huisartspraktijk in drie Europese landen, en zijn er verschillen in de trends in de communicatie tussen huisartsen en patiënten rond het levenseinde met betrekking tot de leeftijd bij het overlijden, het geslacht, het type kanker, de woonplaats in het laatste jaar van het leven en de plaats van overlijden bij kankerpatiënten? (**Hoofdstuk 4**)
4. Hoe evalueren mensen die zorg ontvangen van gespecialiseerde zorgdiensten de informatievoorziening en hun betrokkenheid bij besluitvorming, hoe evalueren nabestaanden van kankerpatiënten die zorg ontvingen van gespecialiseerde zorgdiensten de informatievoorziening, en verschillen deze evaluaties afhankelijk van patiëntkenmerken, duur van de begeleiding en het type palliatieve zorgdienst? (**Hoofdstuk 5**)

De ***derde doelstelling*** (**DEEL III**) is het onderzoeken van beslissingen aan het levenseinde en het daaraan voorafgaande besluitvormingsproces bij mensen die aan kanker zijn overleden. De onderzoeksvraag luidt:

5. Wat is de prevalentie en wat zijn kenmerken van beslissingen rond het levenseinde bij verschillende soorten kanker? (**Hoofdstuk 6***)*

METHODEN

Verschillende dataverzamelingen werden gebruikt om de doelstellingen en onderzoeksvragen van dit doctoraat te beantwoorden.

Cross-sectioneel onderzoek bij mensen met gevorderde kanker: baseline data van een internationale multicentrische cluster-gerandomiseerde trial (Hoofdstuk 2)

Om ***onderzoeksvraag 1*** te beantwoorden, maakten we gebruik van baseline data van patiënten die deelnamen aan de *ACTION-studie*, een multicentrische cluster-gerandomiseerde trial uitgevoerd in 23 ziekenhuizen in zes Europese landen (België, Denemarken, Italië, Nederland, Slovenië, Verenigd Koninkrijk) from 2015 to 2018. Per land en per paar van vergelijkbare ziekenhuizen (academisch of niet-academisch) werden ziekenhuizen willekeurig toegewezen (gerandomiseerd) aan ofwel de interventie-arm, waarin de gebruikelijke (standaard) zorg aanboden aangevuld met een gestructureerd programma van voorafgaande zorgplanning werd aangeboden, ofwel naar de controle-arm, waarin enkel de gebruikelijke zorg aangeboden werd. Bekwaam geachte patiënten met gevorderde longkanker (stadium II of IV) of colorectale kanker (stadium IV) of metachrone metastasen die door leden van hun zorgteam werden aangemerkt als in aanmerking komend, werden geïnformeerd over de studie en uitgenodigd om deel te nemen. Longkankerpatiënten en colorectale kankerpatiënten werden voor de studie geselecteerd omdat deze kankertypes een hoge incidentie en mortaliteit hebben in Europe en beide geslachten treffen. De patiënten werden gevolgd tot één jaar na hun opname in de studie. Zij werden gevraagd een vragenlijst in te vullen 'at baseline', dat wil zeggen op moment van inclusie, voorafgaand aan het starten van het voorafgaande zorgplanning-programma in de interventiegroep – en opnieuw op 11-12 weken, en 19-20 weken na inclusie. In de studie opgenomen in dit doctoraat wordt alleen baseline data gerapporteerd. Behandelend artsen of andere zorgverleners leverden klinische achtergrondinformatie. Alle relevante uitkomstvariabelen werden beoordeeld met behulp van de palliatieve zorg-versie van de European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C15-PAL). Dit meetinstrument is een verkorte versie van de EORTC QLQ-30 kern-vragenlijst voor het meten van kwaliteit van leven bij kankerpatiënten.

Internationale multicentrische longitudinale studie bij mensen met kanker die palliatieve zorg ontvingen (Hoofdstuk 3)

Voor het beantwoorden van ***onderzoeksvraag 2*** hebben we gebruik gemaakt van data afkomstig uit de multicentrische longitudinale *European Palliative Care Cancer Symptom (EPCCS)-studie*. De EPCCS-studie werd uitgevoerd tussen april 2011 en oktober 2013 in 30 palliatieve zorgcentra in 12 landen (Australië, België, Canada, Denemarken, Georgië, Duitsland, Italië, Noorwegen, Portugal, Spanje, Zwitserland en het Verenigd Koninkrijk). Een groot aantal patiënten met gevorderde, ongeneeslijke kanker die waren opgenomen in een palliatief zorgprogramma werd geïncludeerd. Patiënten die een curatieve behandeling ondergingen werden uitgesloten.

De gebruikte data werden verzameld middels een casusformulier waarop een aantal medische gegevens werden ingevuld door zorgverleners (zorgverleners-casusformulier) en door zelfrapportage van participanten over hun gezondheid en symptomen (patiënten-casusformulier). Beide casusformulieren werden maandelijks ingevuld (3-5 weken) gedurende een minimum van drie maanden, of tot aan overlijden of terugtrekking uit de studie. Het casusformulier voor zorgverleners bestond uit een beknopte reeks van medische en behandeling-gerelateerde variabelen, bijvoorbeeld met betrekking tot de primaire kankerdiagnose, comorbiditeiten, de ontvangen behandeling tegen kanker en medicatie. Een retrospectieve registratie van de overlijdensdatum werd uitgevoerd in elk van de studiecentra ongeveer zes maanden na de laatste inclusie in de studie. Het casusformulier voor patiënten bestond uit de meest belangrijke socio-demografische kenmerken, zoals leeftijd, geslacht, burgerlijke staat, woonsituatie en opleiding (verzameld 'at baseline'), en vragen over kwaliteit van leven (KvL) en de ernst van de symptomen. De variabelen die in ons geval van belang waren, waren algehele KvL, emotioneel functioneren, lichamelijk functioneren en kanker-gerelateerde symptomen, welke geëvalueerd werden middels de palliatieve zorg-versie van de European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C15-PAL).

Retrospectieve mortaliteitsstudie bij huisartsen van kankerpatiënten in representatieve epidemiologische surveillancenetwerken (Hoofdstuk 4)

De data die gebruikt werden om ***onderzoeksvraag 3*** te beantwoorden, werden verzameld in België, Nederland en Spanje als onderdeel van de *European Sentinel Network Monitoring End-of-Life Care (EURO SENTIMELC)-studie*. De EURO SENTIMELC-studie is een doorlopende retrospectieve mortaliteitsstudie die ontwikkeld is om retrospectief de zorg rond het levenseinde te kunnen monitoren in bevolkingssteekproeven van overlijdens in verschillende landen. De studie werd uitgevoerd in 2009-2010 (Spanje: 2010-2011) en 2013-2014 bij huisartsen in representatieve 'Sentinel' Netwerken: nationaal representatieve epidemiologische surveillancenetwerken bestaande uit huisartsenpraktijken of wijkartsen die doorlopend de gezondheidsproblemen die zich voordoen in de bevolking monitoren. Deelnemende huisartsen leverden een wekelijks rapport over elke volwassen patiënt in hun praktijk die in de afgelopen week was overleden, als onderdeel van een grotere volksgezondheidsvragenlijst. Wij namen alle door de participerende huisartsenpraktijken geregistreerde patiënten op in onze studie die aan kanker waren overleden (gecodeerd volgens ICD-10) en waarvan het overlijden volgens de huisarts niet 'plotseling en totaal onverwacht' was.

Met behulp van een gestandaardiseerd registratieformulier bestaande uit gestructureerde en gesloten vragen, verzamelden de huisartsen informatie met betrekking tot demografische kenmerken en het kankertype. Bovendien rapporteerden ze voor vijf onderwerpen gerelateerd aan levenseindezorg (diagnose, opties voor zorg rond het levenseinde, psychologische of sociale problemen, de voorkeur van de patiënt met betrekking tot een medische behandeling, de voorkeur van de patiënt met betrekking tot een wettelijk vertegenwoordiger) of deze al dan niet met de patiënt waren besproken.

Nationaal cross-sectioneel onderzoek binnen 34 gespecialiseerde palliatieve zorgteams (Hoofdstuk 5)

Om ***onderzoeksvraag 4*** te onderzoeken, gebruikten we data van een landelijke cross-sectionele enquête die deel uitmaakte van de meer omvattende *Quality Indicators for Palliative Care (QPAC)-studie*. Vragenlijsten werden afgenomen tijdens vier meetperiodes (november 2014, mei 2015, november 2015 en mei 2016) binnen 34 gespecialiseerde palliatieve zorgdiensten.

We gebruikten de vragenlijstitems met betrekking tot informatievoorziening zoals geëvalueerd door patiënten en naasten. Enkel patiënten met een kankerdiagnose werden in de analyses opgenomen. Gegevens van twee verschillende groepen respondenten werden bestudeerd: 1) kankerpatiënten die op het moment van de meting begeleid werden door gespecialiseerde palliatieve zorgdiensten, en 2) naasten van een aan kanker overleden patiënt (bijvoorbeeld de partner, een familielid of een betrokken vriend(in)). De kankerpatiënten en nabestaanden werden geïdentificeerd op basis van de hoofddiagnose en op basis van checklists die werden ingevuld door de coördinatoren van de deelnemende palliatieve zorgteams. Tijdens elke meetperiode werd een cross-sectionele inclusiemethode gebruikt waarbij de palliatieve zorgteams, op de dag van de meting, een willekeurige selectie maakten van twee groepen patiënten met een maximum van 50 in iedere groep: mensen die op die specifieke dag onder begeleiding stonden van een gespecialiseerde palliatieve zorgdienst (zij kregen de patiëntenvragenlijst) en mensen die overleden waren terwijl ze onder begeleiding van een gespecialiseerde palliatieve zorgdienst stonden tussen de afgelopen vier weken en vier maanden (hun naasten kregen de nabestaandenvragenlijst).

De items met betrekking tot informatievoorziening waren ofwel gebaseerd op bestaande vragenlijsten, ofwel ontwikkeld door de onderzoekers in samenwerking met een panel van deskundigen. Items waren voornamelijk afgeleid van de CQ-index Palliative Care, een gestructureerde vragenlijst met vragen over zorgervaringen, en bestaande uit een patiëntenversie en een naastenversie.

Nationaal retrospectief onderzoek onder behandelende artsen op basis van overlijdenscertificaten (Hoofdstuk 6)

Om ***onderzoeksvraag 5*** te beantwoorden, werd gebruik gemaakt van gegevens afkomstig van de *death certificate study on end-of-life decisions (ELD) studie*, gebaseerd op een representatieve steekproef van overlijdens in Vlaanderen, België. Tussen 1 januari en 30 juni 2013 werd wekelijks een willekeurige steekproef van alle overlijdens van Belgische inwoners (van 1 jaar of ouder) getrokken door het Vlaams Agentschap Zorg en Gezondheid. Voor onze analyse werden specifiek de overlijdens uit de databank geselecteerd met een onderliggende oorzaak van kanker. De certificerende artsen kregen binnen twee maanden na het overlijden een vier pagina's tellende vragenlijst toegestuurd via de post, met vragen over medische beslissingen die genomen waren rond het levenseinde, het besluitvormingsproces en de verleende zorg. Zij werden verzocht de vragenlijst in te vullen middels raadpleging van het patiëntendossier. Indien de gecertificeerde arts niet de behandelende arts was, werd de vragenlijst doorgegeven aan de behandelende arts.

Ervan uitgaande dat besluitvorming rond het levenseinde voor het overlijden niet was uitgesloten (dat wil zeggen dat het overlijden niet plotseling en onverwacht kwam, en dat het eerste contact van de arts met de patiënt voor het overlijden plaatsvond), werd aan de artsen gevraagd of zij (1) een potentieel levensverlengde behandeling hadden gestaakt of nagelaten (bijvoorbeeld chemotherapie, of de kunstmatige toediening van voeding en vocht) waarbij zij er rekening mee hielden dat dit het overlijden van de patiënt zou kunnen bespoedigen of de expliciete intentie hadden om dit te doen; (2) pijn/symptoomcontrole hadden geïntensiveerd met gebruik van medicatie met potentieel levensverkortend effect of (3) medicatie hadden toegediend, geleverd of voorgeschreven met de expliciete intentie het overlijden te bespoedigen. Voor patiënten bij wie meer dan één levenseindebeslissing plaats had gevonden, werd de behandeling met de meest expliciete levensverkortende intentie als de meest belangrijke levenseindebeslissing beschouwd. In gevallen waarin twee beslissingen met een gelijkaardige levensverkortende intentie waren genomen, werd prioriteit gegeven aan het toedienen van medicijnen (versus het staken of nalaten van behandeling. Hierna volgden vragen over de redenen voor de belangrijkste levenseindebeslissing en over het besluitvormingsproces. Gegevens over geslacht, leeftijd, plaats van overlijden, en onderliggende doodsoorzaak waren af te leiden van het overlijdenscerficicaat. De onderliggende doodsoorzaak werd gecodeerd aan de hand van de ICD-10.

SAMENVATTING VAN DE BELANGRIJKSTE BEVINDINGEN

DEEL I: Zelf-gerapporteerd emotioneel en fysiek functioneren, symptomen en kwaliteit van leven bij mensen met gevorderde kanker

Patiënt-gerapporteerd emotioneel en fysiek functioneren, symptoomintensiteit en algehele kwaliteit van leven bij mensen met kanker in een gevorderd stadium in verschillende Europese landen

In **Hoofdstuk 2** bestudeerden we emotioneel functioneren, fysiek functioneren, symptoomintensiteit en algehele kwaliteit van leven (KvL) zoals gerapporteerd door een grote representatieve steekproef van mensen met gevorderde long- of colorectale kanker in zes Europese landen. We vergeleken deze patiëntuitkomsten tussen landen. Vermoeidheid kwam naar voren als meest ernstige zelf-gerapporteerde symptoom in deze steekproef. De op één en op twee na slechtst scorende symptomen in termen van ernst waren slapeloosheid en kortademigheid (benauwdheid). We vonden enkele overeenkomsten tussen de verschillende landen. Het verschil tussen het hoogst en laagst scorende land was kleiner dan 10 punten (dit aantal wordt vaak gebruikt als drempel voor klinische relevantie) voor pijn, misselijkheid/braken en constipatie; met andere woorden, de scores voor deze drie symptomen lagen relatief dicht bij elkaar. Naast overeenkomsten vonden we ook verschillende internationale verschillen in functioneren, symptoomintensiteit en KvL. De meest opvallende bevinding was dat de beste scores (dat wil zeggen, de hoogste scores voor emotioneel functioneren en KvL, de laagste voor symptomen) in het algemeen werden gerapporteerd door patiënten uit Nederland en Denemarken, terwijl patiënten uit het Verenigd Koninkrijk relatief minder gunstige uitkomsten rapporteerden. Patiënten uit België rapporteerden een lager emotioneel functioneren vergeleken met het gemiddelde van de overige landen.

De resultaten onderstrepen de essentiële rol van zorgverleners om belastende fysieke en psychologische symptomen consequent op te volgen in de zorg voor patiënten met gevorderde kanker. Beleidsmakers moeten rekening houden met landsverschillen in patiënt-gerapporteerde uitkomsten en investeren in het verlenen van zorg die is afgestemd op de noden van de bevolking. Toekomstig onderzoek moet uitwijzen welke factoren het belangrijkst zijn bij het veroorzaken van deze verschillen tussen Europese landen.

Patiënt-gerapporteerd emotioneel en fysiek functioneren, symptoomintensiteit en kwaliteit van leven in de loop van de tijd bij mensen met gevorderde kanker in Europa

In **Hoofdstuk 3** onderzochten we, in een grote internationale steekproef van mensen met gevorderde kanker die palliatieve zorg ontvingen, de evolutie van functionele status, symptoomintensiteit en de algehele KvL in de loop van de tijd. Patiënt-gerapporteerd emotioneel functioneren, fysiek functioneren, symptomen en KvL bleven over het algemeen stabiel vanaf inclusie (baseline) overheen de tijd gedurende de duur van de studie (≥8-maanden follow-up), zo bleek uit een prospectieve (vooruitblikkende) analyse van de data. Een retrospectieve (terugblikkende) benadering waarin we alleen de patiënten meenamen die tijdens de follow-up overleden waren, wees uit dat emotioneel functioneren aanvankelijk stabiel bleef (bij een vergelijking van patiënten ≥6 maanden voor hun overlijden met patiënten 5-3 maanden voor hun overlijden), maar significant verslechterde in de laatste maanden van het leven (bij een vergelijking van patiënten 5-3 maanden voor hun overlijden met patiënten 2-0 maanden voor hun overlijden). Fysiek functioneren, pijn, vermoeidheid, verlies van eetlust en algehele KvL lieten een progressieve verslechtering zien naar het overlijden toe (patiënten 5-3 maanden voor hun overlijden scoorden slechter dan patiënten ≥6 maanden voor hun overlijden; patiënten 2-0 maanden voor hun overlijden scoorden slechter dan patiënten 5-3 maanden voor hun overlijden). Kortademigheid, slapeloosheid en constipatie verslechterden alleen van 5-3 naar 2-0 maanden voor het overlijden, en misselijkheid/braken vertoonde alleen een significante verslechtering bij een vergelijking van patiënten ≥6 maanden voor hun overlijden met patiënten 2-0 maanden voor hun overlijden.

Uit deze resultaten kan worden geconstateerd dat verslechtering van symptomen reeds kan optreden voor de terminale fase, en geneigd is te versnellen dichterbij het moment van overlijden (‘terminal drop’). De bevindingen benadrukken het belang van vroegtijdige, systematische symptoombeoordeling en -behandeling bij het patiënten met kanker in een gevorderd stadium, en wijzen op de noodzaak voor verder prospectief onderzoek om de factoren te identificeren die het best voorspellen welke patiënten het meest risico lopen op een hoge symptoomlast, en/of een grote beperking in hun functioneren en KvL.

DEEL II: Communicatie rond het levenseinde en informatievoorziening bij mensen met gevorderde kanker

Trends in communicatie over levenseinde-topics met kankerpatiënten in de huisartsenpraktijk in drie Europese landen en verschillen met betrekking tot patiëntkenmerken

Hoofdstuk 4 beschreef een trendanalyse van communicatie over levenseinde-topics met kankerpatiënten in de huisartsenpraktijk in België, Nederland en Spanje in 2009-2010 (Spanje: 2010-2011) en 2013-2014. Een representatieve steekproef van huisartsen registreerde alle overleden volwassen kankerpatiënten in hun praktijk en rapporteerde voor vijf onderwerpen rond levenseindezorg of deze met de patiënten waren besproken. Over het algemeen was diagnose het meest besproken levenseinde-topic in alle drie de landen. In België werden tussen 2009 en 2014 significante stijgende trends gevonden voor communicatie over de diagnose en opties voor zorg aan het einde van het leven, en voor het bekend zijn van huisartsen met de voorkeuren van de patiënt voor medische behandelingen aan het einde van het leven en voor een wettelijke vertegenwoordiger. In Nederland werden tussen 2009 en 2014 significant stijgende trends vastgesteld voor het bekend zijn van huisartsen met de voorkeuren van de patiënt voor medische behandelingen en voor een wettelijke vertegenwoordiger. De stijgende trends in Spanje voor het bekend zijn van huisartsen met de voorkeuren van de patiënten voor medische behandelingen en voor een wettelijke vertegenwoordiger bereikten geen statistische significantie. Naast stijgende trends vonden we voor twee onderwerpen onverwachte dalingen in de tijd. Zowel in Nederland als in Spanje was er een significante afname in de communicatie over opties voor zorg rond het levenseinde en over psychologische en sociale problemen. In het algemeen werden de bovengenoemde trends gezien bij alle patiëntengroepen (leeftijd, geslacht, kankertype, woonplaats in het laatste levensjaar, plaats van overlijden).

Deze bevindingen vertellen ons dat communicatie rond het levenseinde in de eerstelijnszorg in Europa in een relatief korte tijdsspanne aanzienlijk kan veranderen. Ondanks cross-nationale verschillen in de prevalentie en mate/omvang van de verandering, waren er algemene trends zichtbaar die grotendeels vergelijkbaar waren. Uitdagingen met betrekking tot continuïteit van de communicatie tussen huisartsen en patiënten zijn een belangrijk aandachtspunt. Verder onderzoek zou communicatie rond het levenseinde en het proces van voorafgaande zorgplanning in zijn geheel moeten bestuderen, doorheen het gehele ziektetraject, en bij zorgverleners met verschillende specialiteiten uit meerdere settings.

Informatievoorziening door gespecialiseerde palliatieve zorgdiensten en betrokkenheid bij besluitvorming: evaluaties van mensen met kanker en nabestaanden

In **Hoofdstuk 5** werd onderzocht hoe kankerpatiënten die begeleiding kregen van gespecialiseerde palliatieve zorgdiensten in België en hun naasten informatievoorziening en betrokkenheid bij besluitvorming evalueerden. Bovendien onderzochten we hoe familieleden van overleden kankerpatiënten onder begeleiding van gespecialiseerde palliatieve zorgdiensten de informatievoorziening door deze diensten evalueerden, en hoe de evaluaties varieerden met betrekking tot de leeftijd en het geslacht van de patiënt, de duur van de begeleiding, en het type palliatieve zorgdienst. Over het algemeen rapporteerden de meeste patiënten positieve ervaringen met betrekking tot de hoeveelheid informatie die ze kregen over hun ziekte en zorg rond het levenseinde, de mate waarin hun wensen werden gerespecteerd door professionele zorgverleners en de mogelijkheid om te participeren in de besluitvorming over hun zorg. Ook de beoordelingen van nabestaanden waren overwegend positief wat betreft de hoeveelheid informatie die zij ontvingen over de ziekte, de verzorging en het naderende overlijden van de patiënt. De informatievoorziening leek het meest bevredigend voor zowel patiënten als nabestaanden in gevallen waar de zorg werd verleend binnen een aparte palliatieve zorgunit (PCU) in het ziekenhuis – die gepersonaliseerde, continue zorg biedt – in vergelijking met gevallen waar de zorg werd verleend door een mobiel palliatief ondersteuningsteam in het ziekenhuis of een multidisciplinair mobiel palliatief thuiszorgteam – dat voornamelijk ondersteuning en advies verleent aan andere gezondheidszorgprofessionals. We ontdekten ook dat de leeftijd van de patiënt van invloed was op de beoordeling van de besluitvorming. Oudere mensen met kanker hadden vaker een minder actieve rol in het nemen van beslissingen over hun zorg en vonden dat er niet altijd rekening werd gehouden met hun persoonlijke wensen. Familieleden van jongere volwassen patiënten (18-64 jaar) gaven vaker aan minder informatie over de toestand en behandeling van de persoon te hebben ontvangen dan zij nodig achtten dan familieleden van oudere patiënten (65-84 jaar).

Onze resultaten dragen bij aan de bestaande literatuur over de voordelen van gespecialiseerde palliatieve zorgdiensten, door aan de tonen dat diensten goed uitgerust zijn om informatie en ondersteuning te leveren die afgestemd is op de individuele noden van patiënten en families. De bevindingen kunnen helpen bij het optimaliseren van de informatievoorziening en besluitvorming in de kankerzorg binnen de verschillende palliatieve zorgstructuren, en kunnen andere landen informeren in het proces van het verbeteren van hun palliatieve zorgbeleid. Toekomstige studies zijn noodzakelijk om duidelijk te maken hoe diensten kunnen leren van elkaars *best practices*.

DEEL III: Levenseindebeslissingen en het voorafgaande besluitvormingsproces bij mensen die zijn overleden aan kanker

Prevalentie en kenmerken van beslissingen rond het levenseinde bij verschillende soorten kanker

Hoofdstuk 6 concentreerde zich op de prevalentie van beslissingen rond het levenseinde met een mogelijk of zeker levensverkortend effect en kenmerken van het onderliggende besluitvormingsproces bij mensen die waren overleden aan verschillende kankertypes in België. Een nationaal retrospectief onderzoek op basis van overlijdenscertificaten werd uitgevoerd op basis van een grote aselecte steekproef van alle sterfgevallen in Vlaanderen (2013). Behandelend artsen vulden een vragenlijst in over medische beslissingen aan het einde van het leven en het besluitvormingsproces dat leidde tot de levenseindebeslissing. In het algemeen was prevalentie van levenseindebeslissingen (even) hoog bij alle kankertypes. Meer dan één op de tien sterfgevallen (10.4%) was het gevolg van euthanasie of hulp bij zelfdoding door een arts. Dit relatief hoge percentage van geassisteerd sterven was consistent merkbaar in alle kankergroepen (8.7-12.6%). Het toedienen van medicatie met de expliciete intentie de dood te bespoedigen (levensverkortende handelingen) zonder uitdrukkelijk verzoek van de patiënt kwam voor bij 1.8% (1.0-3.4%). De twee redenen die het vaakst door artsen werden opgegeven voor de levenseindebeslissing met de meest expliciete levensbekortende intentie waren lichamelijk lijden en een gebrek aan uitzicht op verbetering. Na correctie voor ‘confounders’, bleken levenseindebeslissingen vaker gebaseerd op verwacht verder lijden en ondraaglijkheid van de situatie voor naaste familieleden bij hematologische kankers dan bij andere soorten kanker. Hoewel patiënten met beslissingsbekwaamheid regelmatig bij het besluitvormingsproces werden betrokken (71.6-92.3%), vond de besluitvorming in bijna 20% van de gevallen nog steeds plaats zonder de inbreng van de patiënt. Opvallend was het lage percentage schriftelijke wilsverklaringen (minder dan 6%) en de suboptimale betrokkenheid van familieleden die we vonden bij patiënten zonder beslissingsbekwaamheid (levenseindebeslissing werd in minder dan 70% van de gevallen besproken met de familie in alle kankergroepen, behalve bij borstkanker). Bij patiënten die niet beslissingsbekwaam waren kon noch de aanwezigheid van een wilsverklaring, noch het al dan niet bespreken van de beslissing worden gerelateerd aan het type kanker.

De bevindingen kunnen erop wijzen dat universele protocollen en training van zorgpraktijken in oncologische settings in België hebben geleid tot een uniforme aanpak van zorg rond het levenseinde en palliatieve zorg. Onafhankelijk van hun specifieke diagnose lijken kankerpatiënten gelijkaardige kansen te krijgen om het proces te doorlopen die nodig zijn om eventueel toegang te krijgen tot praktijken rond geassisteerd sterven. Deze praktijk zijn relatief gebruikelijk binnen de kankerzorg in België. Er is ruimte voor verbetering wat betreft het aanmoedigen van betrokkenheid van patiënten en familieleden bij de besluitvorming. Beleidsmakers moeten strategieën ontwikkelen voor implementatie van programma’s voor voorafgaande zorgplanning en zorginstellingen voorzien van de nodige educatie en middelen.

BESPREKING VAN DE BELANGRIJKSTE BEVINDINGEN

DEEL I: Zelf-gerapporteerd emotioneel en fysiek functioneren, symptomen en kwaliteit van leven bij mensen met gevorderde kanker

De symptoomervaring van patiënten met gevorderde kanker

In de twee grote steekproeven van patiënten met kanker in een gevorderd stadium die in **Hoofdstuk 2** en **Hoofdstuk 3** werden bestudeerd, was vermoeidheid – in overeenstemming met de literatuur – over het algemeen het slechtst scorende (meest ernstige) patiënt-gerapporteerde symptoom. Het is belangrijk hierbij op te merken dat vermoeidheid bij patiënten met gevorderde kanker verschilt van 'normale' vermoeidheid van het dagelijks leven. Het wordt gedefinieerd als een 'onaangenaam, aanhoudend, subjectief gevoel van fysieke, emotionele en/of cognitieve uitputting geassocieerd met kanker of de behandeling van kanker. Andere belangrijke symptomen in termen van ernst waren kortademigheid (benauwdheid), pijn, slapeloosheid en verlies van eetlust, terwijl misselijkheid/braken in beide steekproeven als minder ernstig naar voren kwamen.

Uit eerder onderzoek is gebleken dat kankerpatiënten gedurende hun hele ziektetraject en tot aan het levenseinde symptomen ervaren, en dat deze symptoomlast waarschijnlijk verder toeneemt naarmate de ziekte vordert. Onze bevindingen bevestigen dit door aan te tonen dat sommige symptomen – kortademigheid, slapeloosheid en constipatie – evenals uitkomsten zoals emotioneel functioneren redelijk stabiel lijken te blijven totdat ze relatief kort voor het overlijden verslechteren, terwijl andere symptomen – pijn, vermoeidheid en verlies van eetlust – en uitkomsten zoals fysiek functioneren en algehele KvL 'al' maanden voor de laatste fase van het leven beginnen te verslechteren, hoewel deze verslechtering sneller gaat naarmate het moment van overlijden dichterbij komt. Om deze reden vereist kwalitatieve zorg een systematische evaluatie en behandeling van symptomen tijdens het gehele ziektetraject. Dit kan bijvoorbeeld inhouden dat er routinematig gebruik gemaakt wordt van vragenlijsten waarin de ervaring van de patiënt centraal staat, bekend als patiënt-gerapporteerde uitkomstmaten ('patient-reported outcome measures': PROMs) voor het op systematische wijze opsporen van problemen en noden.

Hoewel de meerderheid van de oncologen van mening is dat een vroegere inschakeling van specialisten in de palliatieve zorg leidt tot een verbetering van de symptoombestrijding, gezondheids-gerelateerde communicatie en continuïteit van zorg, worden patiënten vaak pas laat in het ziektetraject doorverwezen naar palliatieve zorg. Een belangrijke reden voor de onderbenutting van palliatieve zorg in een vroeg stadium is de negatieve connotatie die kleeft aan het label 'palliatieve zorg'. Sommige specialisten hebben daarom opgeroepen tot een *rebranding* van palliatieve zorg om de voordelen ervan bij mensen in allerlei verschillende situaties te benadrukken, het stigma te verminderen en de term meer acceptabel te maken voor betrokkenen.

Verschillende uitdagingen voor verschillende landen in Europa: variëteit in de organisatie van gezondheidszorg

Onze studie beschreven in **Hoofdstuk 2** toonde zowel overeenkomsten als significante verschillen tussen zes verschillende Europese landen in patiënt-gerapporteerde functionele status, symptomen en KvL. Verschillen tussen landen in patiëntuitkomsten kunnen een gevolg zijn van het feit dat de gezondheidszorg en sociale hulpverlening binnen de kankerzorg in verschillende landen anders zijn georganiseerd. Bijna alle Europese landen hebben het afgelopen decennium een nationaal kankerplan aangenomen, maar elk systeem heeft zijn eigen omgeving en context, en heeft zich ontwikkeld onder invloed van historische aspecten, bevolkingskenmerken, gezondheidszorgstructuren en het vroegere en hedendaagse overheidsbeleid. Zo lang een systeem goed presteert, kosteneffectief is en wenselijke uitkomsten/resultaten oplevert, is het niet noodzakelijk om identieke manieren van werken op te leggen. In veel systemen is er echter nog ruimte voor wijziging of verbetering. De prestatie van de gezondheidszorg in verschillende landen kan worden geëvalueerd aan de hand van een aantal indicatoren. Een voorbeeld van zo'n prestatie-indicator is de *beschikbaarheid* van verschillende diensten (bijvoorbeeld de beschikbaarheid van opgeleid personeel voor palliatieve zorg; de wachtlijstijd voor afspraken/consultaties; het aantal diensten waaruit een patiënt kan kiezen). Een ander voorbeeld is de *toegankelijkheid* van gezondheidszorgdiensten (bijvoorbeeld geografische toegankelijkheid; betaalbaarheid; restricties ten gevolge van sociale of culturele barrières; restricties of vertragingen ten gevolge van interne procedures of knelpunten binnen het gezondheidszorgsysteem). Een laatste relevante prestatie-indicator is het *kwaliteits*aspect van de kankerzorg, dat in drie domeinen kan worden onderverdeeld: kwaliteit van de *structuur* (benodigde materiële middelen en 'human resources', organisatorische factoren, toegang tot medische technologieën, beschikbaarheid van multidisciplinaire teams), kwaliteit van het *proces* (het geheel van acties/handelingen waaruit de gezondheidszorg samengesteld is, vormgegeven door klinische en beleidsmatige richtlijnen, gemonitord door kankerregisters en deels tot uiting komend in de tevredenheid van de patiënt), en de kwaliteit van het *resultaat* (kan worden gemeten aan de hand van gezondheids-gerelateerde KvL). In de loop van de tijd is er steeds meer belangstelling ontstaan voor het gebruik van gestandaardiseerde methoden voor het evalueren en beoordelen van uitkomsten en voor het meten van patiënt-gerapporteerde uitkomsten. Er zijn ook meer stappen ondernomen om de kwaliteit van de zorg in verschillende landen te onderzoeken en te 'benchmarken', bijvoorbeeld door de Europese Commissie en door de Organisation for Economic Cooperation and Development (EOCD).

Verschillende uitdagingen voor verschillende landen in Europa: variëteit in cultuur

De waargenomen verschillen tussen de zes in **Hoofdstuk 2** bestudeerde landen – België, Denemarken, Italië, Nederland, Slovenië en het Verenigd Koninkrijk – in patiënt-gerapporteerde functionele status, symptomen en KvL zouden ook (gedeeltelijk) verklaard kunnen worden door verschillen in culturen, ethische, religieuze en politieke achtergronden. Het begrip cultuur is van fundamenteel belang voor de gezondheidszorg op alle niveaus. Cultuur weerspiegelt de manier waarop mensen met kanker hun ziekte en/of de behandeling ervan ervaren en speelt een aanzienlijke rol in de communicatie, interacties met zorgverleners en medische besluitvormingsprocessen. Gezondheidsuitkomsten worden waarschijnlijk ook beïnvloed door 'collectief gezondheidsgedrag' in de vorm van nationaal gezondheidszorgbeleid.

In onze studie scoorden Nederland en Denemarken zeer hoog op emotioneel functioneren en KvL-scores en hadden ze de laagste (meest gunstige) symptoomscores. Van de participerende landen zijn deze landen misschien wel de twee die de meeste overeenkomsten vertonen. Beide landen hebben door de staat gesponsorde, goed functionerende gezondheidszorgsystemen met een goede toegankelijkheid; een protestants-christelijk erfgoed, wat over het algemeen samengaat met een meer progressieve houding ten opzichte van euthanasie vergeleken met de landen met een katholiek erfgoed (zoals België en Italië); en ze behoren consequent tot de top van de gelukkigste landen ter wereld volgens het World Happiness Report. De hoge scores in onze studie zouden een natuurlijk gevolg kunnen zijn van het hoge basisniveau van geluk in deze landen. De meer uiteenlopende scores in andere landen kunnen een weerspiegeling zijn van hun meer gevarieerde achtergronden, maar ook van meer lokale ongelijkheden, zoals de regio of zelfs de specifieke instelling waar de studie plaatsvond. Het Verenigd Koninkrijk liet over het algemeen minder gunstige uitkomsten zien, wat mogelijk te wijten is aan de chronische onderfinanciering van de National Health Service (NHS) en een lager dan gemiddelde uitgave aan gezondheidszorguitgaven op het gebied van kankerzorg.

Het meest waarschijnlijk is dat de variatie tussen landen in onze studie veroorzaakt wordt door een combinatie van verschillen in de prestaties van gezondheidszorgdiensten enerzijds, en verschillen in culturele aspecten anderzijds. Binnen de context en het design van onze studie konden we niet verklaren welk deel van de variatie zou kunnen samenhangen met verschillen in de organisatie van gezondheidszorg en welk deel met cultuurverschillen.

DEEL II: Communicatie rond het levenseinde en informatievoorziening bij mensen met gevorderde kanker

Het bespreken van de diagnose, opties voor zorg rond het einde van het leven en psychologische en sociale problemen in de primaire gezondheidszorg

De relatie tussen arts en patiënt heeft de afgelopen decennia een belangrijke transitie doorgemaakt, van het traditionele, op paternalisme gebaseerde model naar een patiëntgerichte benadering. Een kernelement van deze benadering is gedeelde besluitvorming. Effectieve gedeelde besluitvorming vereist dat patiënten adequaat worden geïnformeerd over hun medische toestand. Zorgverleners hebben de neiging de informatienoden van patiënten te onderschatten en hun kennis en begrip van de ziekte te overschatten. Hoewel patiënten in sommige gevallen liever geen volledige informatie over hun gezondheidstoestand of ernstige diagnose krijgen, geeft een grote meerderheid van patiënten, met inbegrip van kankerpatiënten, er de voorkeur aan gedetailleerde informatie te ontvangen over hun ziekte en de verwachte uitkomsten.

Ofschoon er in verschillende landen en culturen nog steeds op andere manieren wordt omgegaan met vertellen van de waarheid aan patiënten, en zorgverleners vaak terughoudend blijven om informatie over de diagnose (van een gevorderde ziekte) bekend te maken of te bespreken, is er wereldwijd een groeiende tendens om patiënten naar waarheid in te lichten. De meeste westerse landen hebben vandaag de dag een wettelijke verplichting ingevoerd om patiënten eerlijk en naar behoren te informeren over hun aandoening. Deze algemene tendens om met patiënten te spreken over hun diagnose lijkt tot uiting te komen in de hoge percentages van communicatie over het topic 'diagnose' die we in onze studie in alle landen vonden (**Hoofdstuk 4).** We moeten echter voorzichtig zijn in het trekken van vergaande conclusies op basis van deze gegevens, omdat uit onze data niet valt af te leiden of gesprekken over de diagnose bijvoorbeeld wel of niet communicatie en informatie over de prognose omvatten.

Weten huisartsen wat hun patiënten willen en doen ze hier ook iets mee?

De positie van de huisarts in het hart van de gezondheidszorg en de mogelijkheid van een huisarts om een langdurige en doorlopende relatie op te bouwen met zijn/haar patiënten, plaats de huisarts in een sterke positie om communicatie over zorg rond het levenseinde te initiëren en om patiënten en naasten aan te moedigen om te praten over hun persoonlijke noden, waarden en voorkeuren. Volgens onze resultaten lijkt er in de loop van de tijd een algemene trend onder huisartsen te bestaan om beter geïnformeerd te zijn over de voorkeuren van kankerpatiënten voor medische behandeling en het aanwijzen van een wettelijk vertegenwoordiger (**Hoofdstuk 4**). De bevindingen lijken erop te wijzen dat huisartsen zich in toenemende mate bewust worden van (het belang van) deze specifieke aspecten van voorafgaande zorgplanning. Voor een goed geïnformeerde arts die op de hoogte is van de keuze van een patiënt voor een wettelijk vertegenwoordiger, zal het eenvoudiger zijn om de toegewezen persoon binnen een kort tijdsbestek te bereiken om zaken rondom het proces van zorg en behandeling te bespreken. In de door ons uitgevoerde studie werd helaas geen informatie verzameld met betrekking tot het daadwerkelijke gedrag en handelen van de huisarts in relatie tot hun patiënten. Dus als het daadwerkelijk waar is dat huisartsen meer bekend zijn met de wensen van patiënten met betrekking tot behandeling en het aanwijzen van een vertegenwoordiger rond het levenseinde, blijft het tot op heden onbekend of – en op welke manier – zij naar deze kennis handelen.

Men zou ook kunnen aanvoeren dat de waargenomen opwaartse trends slechts de grote lijnen en patronen volgen van groeiende belangstelling voor relatief recente concepten als voorafgaande zorgplanning en patiëntgerichte communicatie in Europa. Beide hebben de laatste jaren meer beleidsaandacht gekregen, in verschillende Europese landen zijn maatregelen genomen in een poging om onderwijs, opleidingen en protocollen op het gebied van palliatieve zorg te verwezenlijken en implementeren. De twee vragenlijstitems die opgenomen werden in onze analyse zijn echter zeer specifiek van aard en vertegenwoordigen slechts een fractie van het veelomvattende begrip voorafgaande zorgplanning. Deze items kunnen daarom niet gebruikt worden om uitspraken te doen over het gehele proces.

Het belang van effectieve communicatie en informatie-uitwisseling tussen professionals in de primaire en secundaire gezondheidszorg

Onze resultaten lieten een dalende trend zien in de communicatie tussen huisartsen en patiënten over de topics opties voor zorg rond het einde van het leven en over psychologische en sociale problemen. Een verklaring hiervoor zou kunnen liggen in het fenomeen van toenemende specialisatie en taakdifferentiatie in de eerste- en tweedelijnszorg. Uit de literatuur blijkt dat kankerpatiënten vanuit de huisartsenpraktijk kunnen ‘verdwijnen’ in de richting van ziekenhuizen, waar ze tijdens en na hun behandeling meer tijd spenderen onder specialistische zorg. Dit betekent dat gesprekken over zorgopties bij een naderend levenseinde en over psychologische of sociale kwesties mogelijk steeds vaker plaatsvinden met bijvoorbeeld gespecialiseerde oncologisch verpleegkundigen in ziekenhuizen.

Kwalitatief onderzoek naar de positie van huisartsen in de continue primaire zorg rond het levenseinde toont aan dat mensen die terminaal ziek zijn de huisarts vaak een prominente rol toekennen in diverse aspecten van twee vormen van continuïteit. ‘Relationele continuïteit’ verwijst naar het waarborgen van een gecontinueerde relatie van een patiënt met dezelfde huisarts. Voorbeelden hiervan zijn contact houden met de patiënt na verwijzing en een verantwoordelijkheidsgevoel koesteren ten opzichte van de patiënt. ‘Informatieve continuïteit’ verwijst naar het aanwenden van patiëntgegevens, zoals zijn of haar voorgeschiedenis of individuele omstandigheden, om op die manier gepersonaliseerde zorg op maat te kunnen bieden. Van essentieel belang hierbij is een goede uitwisseling van informatie tussen huisartsen, specialisten en zorginstellingen. De kwalitatieve data liet zien dat wanneer meerdere disciplines uit de eerstelijns- en tweedelijnszorg betrokken bij de zorg voor een patiënt, in het speciaal gespecialiseerde artsen, dit kan makkelijk leiden tot fouten en miscommunicatie waardoor een meer actieve houding van de patiënten en naasten zelf nodig is. Sommige patiënten rapporteerden ook een gebrek aan coördinatie, waardoor het onduidelijk was wie hun centrale contactpersoon was en dit zorgde voor stress. Dit beklemtoont de noodzaak van frequente communicatie tussen huisartsen en overige zorgverleners, zelfs in gevallen waarin één bepaalde rol (zoals de huisarts) door de patiënt wordt beschouwd als het meest centrale contactpunt voor zorg.

Ervaringen van Belgische kankerpatiënten en naasten met betrekking tot informatievoorziening en betrokkenheid bij besluitvorming in gespecialiseerde palliatieve zorg

Zoals beschreven in **Hoofdstuk 5**, was een grote meerderheid van mensen met kanker die zorg ontvingen van gespecialiseerde palliatieve zorgdiensten, en nabestaanden van kankerpatiënten die waren overleden terwijl zij onder begeleiding stonden van gespecialiseerde palliatieve zorgdiensten, over het algemeen tevreden over de informatievoorziening, waarbij ze aangaven dat ze 'precies de juiste hoeveelheid' informatie hadden ontvangen over de ziekte en (levenseinde) zorg. Ook de betrokkenheid van patiënten bij de besluitvorming werd over het algemeen positief beoordeeld. Uit voorgaande studies is gebleken dat kankerpatiënten vaak melding maken van onvervulde/onbeantwoorde noden op het gebied van informatievoorziening, en dat informatie over palliatieve zorg of zorg aan het levenseinde vaak niet wordt verstrekt, zelfs niet wanneer de patiënt in een gevorderd stadium van zijn/haar ziekte verkeert. In België bepaalt de wet betreffende de rechten van de patiënt die op 22 augustus 2002 in werking is getreden dat de patiënt het recht heeft om geïnformeerd te worden – maar ook het recht om *niet* geïnformeerd te worden op zijn/haar nadrukkelijk verzoek. Ons onderzoek suggereert dat de kans dat tegenmoet wordt gekomen aan de informatienoden van patiënten met gevorderde kanker en hun naasten groter lijkt te zijn in een omgeving van gespecialiseerde zorg; echter waren niet alle gespecialiseerde zorgdiensten precíes even succesvol. In overeenstemming met eerdere bevindingen uit de literatuur vonden we dat informatievoorziening meer bevredigend was voor zowel de patiënten als naasten wanneer de patiënt zorg ontving binnen de context van een in het ziekenhuis gevestigde palliatieve zorgeenheid dan wanneer de patiënt werd ondersteund door gespecialiseerde zorgteams die met name optreden als 'consultants' en support en advies bieden aan andere zorgverleners. De structuur van in het ziekenhuis gevestigde palliatieve zorgeenheden lijkt het meest effectief in het faciliteren van een ondersteunde omgeving voor optimale informatievoorziening, waarschijnlijk omdat patiënten en naasten hier op een meer *directe* en *'op maat gesneden'* manier worden benaderd en geïnformeerd.

Gedeelde besluitvorming in de kankerzorg: worden ouderen gehoord?

'Agisme' – vooroordelen, stereotypering en discriminatie op basis van leeftijd – is een wereldwijd probleem, dat in alle landen veelvuldig voorkomt en dat met de vergrijzing waarschijnlijk nog verder zal toenemen. Het kan tot uiting komen in de klinische praktijk en in besluitvormingsprocessen, en kan de gezondheid en het welzijn van mensen aanzienlijk beïnvloeden. In het algemeen worden oudere patiënten minder vaak actief betrokken bij medische besluitvorming dan jongere patiënten. Ook wordt er minder vaak rekening gehouden met hun persoonlijke zorgwensen, zoals ook bleek uit ons onderzoek (**Hoofdstuk 5**). De veronderstelling van artsen dat oudere kankerpatiënten minder informatie wensen en beslissingen wensen over te laten aan hun zorgverleners, blijkt een belangrijke barrière te zijn voor deelname van oudere patiënten aan gedeelde besluitvorming. Zorgverleners zijn geneigd om zich te richten tot de jongere familieleden, waardoor de oudere patiënt wordt overgeslagen. Vaak zijn zorgverleners zich niet bewust van een discriminerende houding in hun communicatiestijl, of ze gaan er gewoonweg vanuit dat jongere familieleden sneller zijn als het gaat om het horen en begrijpen van informatie. Dit kan leiden tot ongelijkheid in de kwantiteit en de kwaliteit van de zorg die aan oudere patiënten wordt verleend, en bijgevolg ook in hun gezondheidsuitkomsten. Actieve betrokkenheid bij besluitvorming wordt in verband gebracht met positieve uitkomsten op het vlak van gezondheid, zoals een betere KvL en een beter lichamelijk en sociaal functioneren. Mensen die actief deelnemen aan het besluitvormingsproces zijn doorgaans beter geïnformeerd, kunnen de voordelen en risico's van bepaalde keuzes beter inschatten en ervaren minder beslissingsambivalentie en ontevredenheid.

Wel moet hierbij opgemerkt worden dat verschillende studies laten zien dat oudere patiënten geneigd zijn de voorkeur te geven aan een minder actieve rol in medische besluitvorming, terwijl jongere patiënten over het algemeen meer betrokkenheid of een gedeelde rol wensen. Patiënten 'pushen' om actief deel te nemen aan besluitvorming als ze dat niet willen kan nadelige gevolgen hebben, zoals spijt van genomen beslissingen, toename van angst, gebrek aan vertrouwen in de besluitvorming en stress. Een lagere participatievoorkeur kan echter ook voortkomen uit de angst niet competent genoeg te zijn om een zinnige bijdrage aan de discussie te leveren of de angst om voor vertraging in het gesprek te zorgen. Dit kan nog sterker het geval zijn wanneer patiënten een lage 'gezondheidsgeletterdheid' (*health literacy*) hebben, wat vaker voorkomt bij ouderen. Artsen zullen meer tijd moeten besteden aan de communicatie met oudere kankerpatiënten om hen te helpen inzicht te krijgen in hun keuzes en het gewenste level van betrokkenheid bij de besluitvorming, en om beter in staat te zijn hun unieke doelen, waarden en voorkeuren te respecteren en hierop in te spelen – de hoeksteen voor effectieve patiëntgerichte zorg.

DEEL III: Levenseindebeslissingen en het voorafgaande besluitvormingsproces bij mensen die zijn overleden aan kanker

Suboptimale betrokkenheid van kankerpatiënten en hun naasten bij besluitvorming rond het levenseinde in België

In geval van terminale ziekte kunnen patiënten, familieleden en zorgverleners voor een aantal complexe, gevoelige beslissingen komen te staan die genomen moeten worden over behandeling en zorg rond het einde van het leven. Daartoe behoren beslissingen rond het levenseinde die het overlijden van de patiënt kunnen bespoedigen, hetzij impliciet (wanneer de dood een verwacht, maar onbedoeld gevolg is van de medische beslissing), hetzij – minder vaak – expliciet (wanneer de dood het beoogde gevolg is van de beslissing). Uit onze bevindingen bleek dat in ongeveer 20% van de gevallen waarin de patiënt op dat moment wilsbekwaam werd geacht, deze niettemin niet betrokken was bij het besluitvormingsproces dat aan de levenseindebeslissing voorafging. Hoewel dit percentage in de loop van de tijd lijkt te zijn verbeterd in vergelijking met eerdere studies, is het nog steeds suboptimaal. Een mogelijke verklaring kan liggen in het feit dat gesprekken over het levenseinde nog altijd vaak als zwaar en stressvol worden gezien voor zowel de arts als de patiënt. Artsen kunnen zich er ongemakkelijk bij voelen om het gesprek aan te gaan met hun patiënten over het gestigmatiseerde onderwerp sterven en dood. Het kan ook zijn dat ze geen ervaring hebben met dergelijke gesprekken, of dat de instrumenten, richtlijnen en training rond communicatie over het levenseinde waarover ze beschikken ontoereikend zijn. Een andere mogelijkheid is dat bepaalde levenseindebeslissingen, met name 'intensivering van de verlichting van pijn en symptomen', zo gewoon zijn geworden in de kankerzorg, dat artsen het niet altijd nodig achtten om ze te bespreken. Nochtans moeten, conform het principe van respect voor de autonomie van de patiënt, alle mogelijk levensverkortende handelingen met de patiënt worden besproken, tenzij hij of zij uitdrukkelijk anders heeft aangegeven. De bevindingen van dit proefschrift onderstrepen het belang voor artsen en andere zorgverleners om patiënten te blijven aanmoedigen om actief deel te nemen aan het besluitvormingsproces, rekening houdend met de individuele voorkeuren van patiënten voor de mate van participatie in beslissingen over behandelingen rond het levenseinde.

Hoewel het respecteren van de wensen van de patiënt bij de besluitvorming van primair belang is, kunnen ook naasten van de patiënt een belangrijke bijdrage leveren aan het besluitvormingsproces. Palliatieve zorg moet gericht zijn op het verbeteren van de kwaliteit van leven van *zowel patiënten als hun naasten* die met een levensbedreigende ziekte worden geconfronteerd. Daarom wordt het betrekken van familieleden en andere belangrijke personen uit de naaste omgeving van een stervende patiënt bij de besluitvorming beschouwd als 'good practice' voor artsen en andere beroepsbeoefenaren in de gezondheidszorg. Betrokkenheid van familieleden bij de besluitvorming wordt nog belangrijker wanneer de patiënt wilsonbekwaam wordt. Onze resultaten toonden aan dat wanneer de patiënt wilsonbekwaam was, familieleden in minder dan 70% van de gevallen bij de besluitvorming werden betrokken (bij alle soorten kanker, behalve bij borstkanker waar dit percentage iets hoger was). Aangezien uit eerder onderzoek is gebleken dat de overgrote meerderheid van kankerpatiënten wenst dat hun naasten betrokken worden bij medische beslissingen rond het levenseinde, met name in geval van verlies van competentie, wijzen de bevindingen van onze studie erop dat er nog ruimte is voor verbetering.

Hoog aantal gevallen van euthanasie of hulp bij zelfdoding door een arts bij gevorderde kanker in België

Onze resultaten toonden aan dat het aantal levenseindebeslissingen ongeveer even hoog was bij de vijf meest voorkomende kankersoorten (gastro-intestinaal, long, genito-urinair, borst, hematologisch). Meer dan één op de tien in 2013 geregistreerde sterfgevallen door kanker (10,4%) was het gevolg van euthanasie of door een arts begeleide zelfdoding. Dit is een belangrijke stijging als we dit percentage vergelijken met de 5,6% van alle sterfgevallen door kanker ten gevolge van euthanasie die in 2007 werd geregistreerd. Uit de bevindingen kunnen we afleiden dat praktijken rond stervensbegeleiding wijdverspreid zijn binnen de kankerzorg in België. In het algemeen lijken kankerpatiënten gelijke kansen te hebben om toegang te krijgen tot euthanasie en de procedures hiervoor te doorlopen, ongeacht hun specifieke kankerdiagnose. Op maatschappelijk niveau is dit een aanwijzing dat geassisteerd sterven vrij goed is ingebed in de zorg aan het einde van het leven van kankerpatiënten. Uiteraard hangen beslissingen rond het levenseinde sterk samen met het gezondheidszorgsysteem en het regelgevend kader in een land. België was het tweede land in Europa dat in 2002 euthanasie legaliseerde, in specifieke omstandigheden en onderworpen aan wettelijke waarborgen. De schijnbaar brede integratie van euthanasie in de zorg aan het einde van het leven voor kankerpatiënten in België kan een gevolg zijn geweest van opleiding en klinische ondersteuning van medisch personeel door 'Life End Information Forum' (LEIF) artsen, maar ook van het voortdurende debat over euthanasie in de media sinds de legalisatie, wat kan hebben geleid tot een groter bewustzijn van de rechten van terminaal zieken en tot een toegenomen maatschappelijke aanvaarding van euthanasie.

Het is echter belangrijk op te merken dat er weinig bewijs is over hoe goed euthanasie is geïntegreerd in de palliatieve zorg in België. Bovendien kan de relatie tussen euthanasie en palliatieve zorg hypothetisch twee richtingen uitgaan. Goede palliatieve zorg zou het aantal verzoeken van patiënten kunnen verminderen als gevolg van een goede symptoomcontrole die resulteert in minder lijden, maar zou ook juist kunnen leiden tot een groter aantal euthanasieverzoeken door terminaal zieke patiënten als gevolg van toegenomen communicatie en het creëren van een veilige omgeving.

Relevantie van dit proefschrift in het licht van recente ontwikkelingen in kankertherapieën

Voor vier van de vijf studies (**Hoofdstuk 3-6**) die in dit proefschrift worden gepresenteerd en besproken, vond de gegevensverzameling meer dan vijf jaar geleden plaats. In de afgelopen tien jaar is er een aanzienlijke vooruitgang geboekt op het vlak van de behandeling van kanker. Vormen van immuuntherapie zijn al succesvol gebleken bij de behandeling van veel soorten kanker, en kunnen – alleen of in combinatie met conventionele behandelingen – het leven van mensen met gevorderde stadia van kanker verlengen. Dit doet niets af aan het belang van (tijdige) betrokkenheid van palliatieve zorg, die geheel gebaseerd moet zijn op wat patiënten *nodig* hebben, onafhankelijk van prognose of behandelingsintentie. Mensen die langdurig overleven met ongeneeslijke kanker kunnen grote variaties vertonen in hun behoefte aan palliatieve zorg. Onderzoek heeft aangetoond dat patiënten fysieke, emotionele en existentiële problemen kunnen ervaren tijdens de levensverlengende fase van de behandeling. Daarom blijven, ongeacht de recente ontwikkelingen, het optimaliseren van KvL en het verlichten van het lijden primaire doelen van de behandeling.

De WHO formuleert palliatieve zorg ook als een benadering waarbij oncologische zorg en palliatieve zorg worden geïntegreerd of parallel worden gegeven. ‘*… Het is toepasbaar in een vroeg stadium van de ziekte, in combinatie met andere therapieën als doel hebben het leven te verlengen*.’ Palliatieve zorgnoden moeten worden beoordeeld als een continu proces vanaf de diagnose. Wanneer kankerbehandeling en palliatieve zorg gelijktijdig worden verstrekt, profiteren patiënten van de deskundigheid van zowel oncologische als palliatieve zorgteams – extra belangrijk in dit tijdperk van nieuwe kankertherapieën, aangezien immuuntherapie minder toxisch is en hierdoor geschikter voor mensen die dichter bij het einde van hun leven zijn dan standaardbehandelingen. Wanneer de behandeling gericht is op genezing of op verlenging van het leven, kan de meeste zorg tijdens het ziekteproces op generalistisch niveau worden verleend door gezondheidsmedewerkers met basiscompetenties in palliatieve zorg – in deze context voornamelijk oncologen. Aangezien kanker meer en meer een chronisch karakter heeft, wordt ook steeds meer erkend dat generalistische eerstelijnszorgverleners (huisartsen, wijkverpleegkundigen) een centrale plaats innemen in de kankerbestrijding. Als symptomen zeer moeilijk beheersbaar worden, zullen generalistische zorgverleners advies inwinnen bij of doorverwijzen naar gespecialiseerde palliatieve zorgdiensten.

IMPLICATIES EN AANBEVELINGEN

Uitdagingen en suggesties voor toekomstig onderzoek

1) Meer diepgaand onderzoek naar de oorzaken van de landsverschillen in belangrijke patiënt-gerapporteerde uitkomsten

Beroepsbeoefenaren in de gezondheidszorg en beleidsmakers in de kankerzorg hebben hetzelfde essentiële doel: ervoor zorgen dat mensen met kanker die gezondheidszorg nodig hebben de best mogelijke zorg krijgen, op de juiste plaats en op het juiste tijdstip, waarbij rekening wordt gehouden met hun behoeften en voorkeuren. Desalniettemin is gebleken dat het verbeteren van de kwaliteit van de kankerzorg voor veel landen een serieuze uitdaging is en dat er tussen de landen onderling nog steeds aanzienlijke verschillen in zorguitkomsten bestaan. Onze resultaten onderstrepen dit, aangezien we duidelijke verschillen vonden in de patiënt-gerapporteerde functionele status, symptoomintensiteit en algehele KvL bij patiënten uit verschillende Europese landen. Er zijn allerlei mogelijke factoren die aan deze bevindingen zouden kunnen bijdragen. De verschillen kunnen bijvoorbeeld het gevolg zijn van de heterogeniteit van nationale gezondheidszorgsystemen en de organisatie van de gezondheidszorg in de verschillende landen, verschillen in culturele praktijken en attitudes, en verschillen in de opleiding, de financiering en de nationale culturen inzake palliatieve zorg. De opzet van de huidige studie liet niet toe om duidelijke conclusies te trekken over de onderliggende systemische redenen. Aangezien een beter begrip van deze redenen en verklaringen richting zou kunnen geven aan eventuele verdere stappen, zijn wij van mening dat dit een belangrijk gebied is voor verder onderzoek.

2) Longitudinaal onderzoek om factoren te identificeren die voorspellers zijn van belangrijke patiënt-gerapporteerde uitkomsten en hun ontwikkeling in de loop van de tijd

Dankzij de vooruitgang die de afgelopen decennia bij de behandeling van kanker is geboekt, leven steeds meer mensen voor een langere periode met kanker die als ongeneeslijk wordt beschouwd. Tijdens hun ziektetraject komen deze mensen voortdurend voor moeilijke uitdagingen te staan bij het stellen en verschuiven van persoonlijke doelen en bij het plannen van hun zorg om deze doelen te bereiken. Dit is de reden waarom longitudinale onderzoeksdesign met een langdurige tijdspanne en grote hoeveelheden data zo belangrijk zijn: zij stellen ons in staat bepaalde patronen te herkennen en vast te stellen, wat niet mogelijk is met korte-termijn onderzoek. Ons onderzoek naar het verloop van emotioneel functioneren, lichamelijk functioneren en symptoomintensiteit bij palliatieve kankerpatiënten was exploratief van aard en richtte zich niet specifiek op factoren die mogelijk samenhangen met de evolutie van deze patiëntuitkomsten in de loop van de tijd. We konden dus niet achterhalen wat patiënten met verschillende niveaus van functionele beperkingen, symptomatologie en KvL, karakteriseert gedurende het verloop van de ziekte tot aan het overlijden. Dit benadrukt de noodzaak van verdere prospectieve studies om de factoren te identificeren die voorspellen welke patiënten het meeste risico lopen op een hoge symptoomlast, en die gericht kunnen worden aangepakt om ongunstige patiënten-uitkomsten te voorkomen.

3) Onderzoek naar voorafgaande zorgplanning bij kankerpatiënten en verschillende gezondheidszorgprofessionals gedurende het gehele ziektetraject

Patiëntgerichte communicatie en voorafgaande zorgplanning hebben de laatste jaren toenemende beleidsaandacht gekregen in Europa. In dit proefschrift keken we naar trends in de prevalentie van huisarts-patiënt gesprekken over bepaalde onderwerpen rond het levenseinde. Onze studie rapporteerde echter alleen of onderwerpen werden besproken volgens de huisarts, en dit vertegenwoordigt niet de volledige complexiteit van communicatie rond het levenseinde met kankerpatiënten. Door de voortdurende toename van de specialisatie van kankerzorg en palliatieve zorg, is het mogelijk dat bepaalde onderwerpen vaker worden besproken met palliatieve zorgverleners in plaats van met huisartsen. Toekomstig onderzoek zou een vollediger beeld moeten geven door het proces van voorafgaande zorgplanning in zijn geheel te bestuderen doorheen het gehele ziektetraject en aan de hand van de perspectieven van patiënten en hun familie, alsook de verschillende betrokken zorgverleners op alle zorgniveaus mee te nemen.

Implicaties en aanbevelingen voor klinische praktijk en beleid

1) Routinematige evaluatie van patiënt-gerapporteerde uitkomsten als standaardonderdeel van de kankerzorg gedurende het gehele ziektetraject

Onze bevindingen bevestigen dat de optimalisatie van symptoomcontrole, functionele status en KvL een uitdaging blijft voor zorgverleners in de palliatieve kankerzorg in alle Europese landen, en dat dit een nog moeilijkere klus wordt in latere stadia van het ziektetraject, als het levenseinde nadert. Daarom onderstrepen we het belang van de implementatie van periodieke, subjectieve evaluaties van patiënt-gerapporteerde uitkomsten als standaard onderdeel van het werk van zorgverleners in de kankerzorg.

Patiënt-gerapporteerde uitkomstmaten (PROMs) worden in toenemende mate gebruikt in klinische settings voor het monitoren van de symptomen, noden en progressie van individuele patiënten doorheen het zorgtraject. PROMs hebben een scala aan voordelen. Jammer genoeg zijn ze zelden ingebed als standard onderdeel van routinematige oncologische zorg. Technologische vooruitgang heeft geleid tot de ontwikkeling van elektronische systemen om het verzamelen en rapporteren van patiënt-gerapporteerde resultaten in verschillende settings te vergemakkelijken. Elektronische PROMs (ePROMs) maken een onmiddellijke weergave van interpreteerbare resultaten voor de clinicus mogelijk en vergemakkelijken de opslag, koppeling en overdracht van patiëntresultaten, wat de communicatie en informatieoverdracht tijdens consultaties ten goede komt.

2) Bevorderen van sterke samenwerkingsverbanden tussen verschillende beroepsgroepen in verschillende zorgsectoren om de uitwisseling van informatie en continuïteit van zorg te ondersteunen

Palliatieve zorg heeft per definitie een multidisciplinair karakter. Bijgevolg kan de samenwerking en coördinatie van palliatieve zorg zeer complex zijn. Er zijn tal van disciplines bij betrokken en er is sprake van verschillende overgangen tussen verschillende locaties en zorgniveaus gedurende het ziektetraject. Dit kan leiden tot onderbrekingen in de continuïteit van zorg en informatie. Om een effectieve arts-patiëntrelatie te behouden en de continuïteit van de zorg te waarborgen, moeten huisartsen pro-actiever zijn in het onderhouden van contact met hun patiënten na diagnose. Tegelijkertijd moeten gespecialiseerde zorgverleners de verantwoordelijkheid op zich nemen om de huisartsen op de hoogte te houden van de zorg voor hun patiënten. De samenwerking kan verder worden vergemakkelijkt middels het gebruik van elektronische patiëntendossiers, waardoor de toegang van huisartsen tot patiëntinformatie en de informatieoverdracht tussen de generalistische en specialistische zorgsetting waarschijnlijk sterk kunnen verbeteren. De ondersteuning die geboden wordt in de context van palliatieve zorgeenheden in ziekenhuizen, die zowel door patiënten als door naasten hoog wordt gewaardeerd, zou door andere gespecialiseerde diensten als 'benchmark' voor hun prestaties op het gebied van zorg kunnen worden gebruikt. Om de zorg te verbeteren en beroepsgroepen in staat te stellen van elkaars 'best practices' te leren, is het creëren en koesteren van optimale samenwerking tussen zorgverleners een belangrijk aandachtsgebied voor beleidsmakers.

3) Investeren in onderwijs en opleiding voor toekomstige en huidige gezondheidswerkers in de palliatieve kankerzorg om interprofessionele samenwerking te bevorderen

In de vorige aanbeveling werd gewezen op de noodzaak van sterke samenwerkingsrelaties tussen zorgverleners uit verschillende zorgkaders als sleutelfactor voor het behoud van de continuïteit van zorg voor mensen met kanker tijdens de actieve behandeling, de ondersteunende zorg, de palliatieve zorg, de overleving of de zorg aan het einde van het leven. Interprofessionele samenwerking is een fundamentele competentie die krachtig ondersteund moet worden op beleidsniveau, en dit vraagt om meer onderwijsinspanningen. Om de kankerzorg in het hele zorgtraject op grotere schaal te verbeteren, moet interprofessionele samenwerking meer aandacht krijgen en voldoende geïntegreerd worden in de curricula van alle basisopleidingen (bijvoorbeeld geneeskunde, verpleegkunde, maatschappelijk werk) en gespecialiseerde postdoctorale opleidingen (bijvoorbeeld voor huisartsen, oncologen, artsen voor palliatieve zorg, oncologieverpleegkundigen).

4) Toepassen van strategieën om de betrokkenheid van patiënten en familie bij levenseindebeslissingen met een potentieel levensverkortend effect te verbeteren

Betrokkenheid van de patiënt bij de medische besluitvorming wordt beschouwd als een cruciaal onderdeel van patiëntgerichte zorg en wordt zelfs nog belangrijker wanneer een patiënt het einde van zijn leven nadert. De meerderheid van kankerpatiënten wil betrokken worden bij beslissingen over zorg aan het einde van het leven. Onze bevindingen toonden echter aan dat volgens hun artsen 20% van de competente (beslissingsbekwame) kankerpatiënten niet betrokken waren bij het besluitvormingsproces voorafgaand aan beslissingen over het levenseinde. Ook werd minder dan 70% van de familieleden betrokken bij het besluitvormingsproces in gevallen waarin de patiënt incompetent (niet beslissingsbekwaam) werd geacht, hoewel uit eerder onderzoek bekend is dat de meeste kankerpatiënten willen dat hun familieleden participeren in de medische besluitvorming rond het levenseinde, vooral wanneer de patiënt niet meer zelf in staat is om beslissingen te nemen.

Er zijn verschillende barrières voor zorgverleners om patiënten en hun familieleden actief te betrekken bij besluitvorming rond het levenseinde, zoals weerstand van professionele zorgverleners of patiënten om dit te doen, onvoldoende gelegenheid of tijd om hierover te spreken, een gebrek aan training bij de zorgverleners, een gebrekkig begrip van de belangrijke rol van familieleden, niet weten met wie te praten, of het niet snel genoeg in contact kunnen komen met de juiste mensen in een dringende situatie. De toewijzing van een centrale contactpersoon die een directe communicatielijn heeft met de arts van de patiënt om, indien nodig, zorg en behandeling te bespreken, zou deel moeten uitmaken van de standaard kankerzorg. Contactgegevens voor noodgevallen en back-up moeten al vroeg in het ziektetraject in het dossier aanwezig zijn en voor de verscheidene zorgverleners toegankelijk zijn.

Voor beleidsmakers zou het van nut kunnen zijn om de evolutie van de betrokkenheid van patiënten en familie bij levenseindezorg en levenseindebeslissingen nauwlettend te volgen gedurende een langere tijdsperiode. Mogelijke veranderingen in de loop van de tijd zouden zorgverleners en zorgmanagers kunnen informeren over de noodzaak eventuele acties te ondernemen, waarbij bijvoorbeeld gedacht kan worden aan het verbeteren van onderwijs en processen, zowel in de ziekenhuisomgeving als daarbuiten.

C

Curriculum vitae

ABOUT THE AUTHOR

Mariëtte Nadine Verkissen was born on the 24th of November 1986 in Venlo, the Netherlands. She has a Bachelor's degree in Psychology (2011, cum laude) and a Master's degree in Medical Psychology (2013, with distinction) from Tilburg University, the Netherlands. The track she followed within the two-year Medical Psychology Master's program concentrated on scientific research. After spending a period at the Comprehensive Cancer Center South (Integraal Kankercentrum Zuid) in Eindhoven to complete a research internship, and to write a Master's thesis on the role of health literacy in perceived information provision and satisfaction among women with ovarian tumors, she was motivated to start doing PhD research in the field of (social) health sciences. In November 2013, after completing her Master's, she moved to Belgium to join the End-of-Life Care Research Group, Vrije Universiteit Brussel & Ghent University as a junior researcher. For several years, she has worked as an executive researcher of the Flemish part of the EU FP7-funded ACTION project, a large multi-center trial conducted in six European countries with the primary aim of studying how formalized advance care planning (ACP) affects quality of life and symptoms among advanced lung- or colorectal cancer patients. Alongside her responsibilities for ACTION, she has been exploring and analyzing secondary data from various other research projects to study the topics of symptom burden, quality of life, communication and end-of-life care in advanced cancer patients as part of her PhD trajectory. The results reported and discussed in this dissertation were published in five international peer-reviewed journals and presented at a number of national and international conferences. At this moment, Mariëtte still lives in Ghent together with the sweetest and possibly laziest cat in existence, Pippa.

P

List of publications and presentations

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