Olaf Geerse

THE IMPACT OF LUNG CANCER

Towards high-quality and patient-centered supportive care

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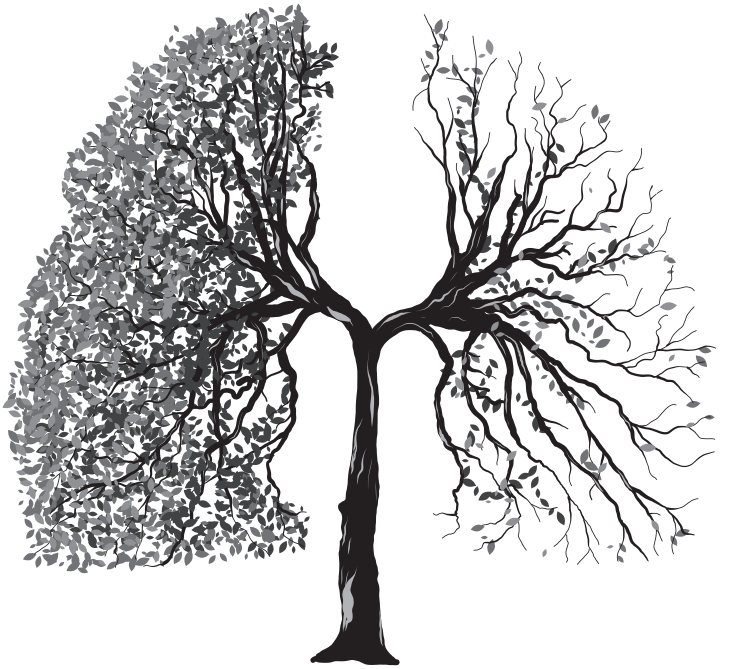

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Guérir quelquefois, soulager souvent, consoler toujours.
To cure sometimes, to relieve often, to comfort always.

Edward Livingstone Trudeau (American physician, 1848 – 1915)

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Chapter 1

General introduction

INTRODUCTION

Lung cancer remains one of the most frequently diagnosed cancers worldwide.[1–3] Despite recent advances in treatment modalities, the disease can be devastating for patients, their loved ones, and for clinicians in trying to provide the best clinical care for these patients.[4] Likely factors contributing to this are the poor prognosis and subsequent outcomes that most patients face after their diagnosis, the multitude of comorbidities such as heart failure or advanced chronic obstructive pulmonary disease (COPD) that make the disease difficult to manage, and a diagnosis that is often established relatively late in the disease course.[5] Further, the disease and subsequent treatments impacts all aspects of daily living and often affects caregivers and loved ones as well.[6,7]

Patients with lung cancer and their caregivers enter an increasingly complex and fragmented health care system at the time of diagnosis and thereafter.[8] Issues regarding communication between different healthcare providers and lack of access to a single point of care within the hospital may hamper the optimal delivery of care.[6] Further, the main focus of care, especially in larger academic settings, may often primarily be on medical treatment of the disease rather than the provision of supportive care for patients and caregivers. This may lead patients to feel isolated with their concerns or personal wishes and preferences regarding their future care as well as distressing physical or emotional symptoms.[7,9–12] Although the many recent treatment advances in lung cancer should clearly be applauded,[4,13,14] these advances also require us to better rethink the complex organization of personalized cancer care.

One integral component enabling the optimal delivery of care is development and structural embedding of supportive care services both throughout and after treatment.[15,16] The primary focus of this line of care is on preventing or relieving distressing symptoms caused by a serious illness and optimizing the quality of life (QoL) of patients as well as their caregivers.[17] Further, this care is multidisciplinary by nature, not restricted to oncological conditions, and should be provided at multiple time points during and after a person's illness to ensure care concordant with personal preferences as well as pain and symptom relief. In this thesis, we focus primarily on patients with lung cancer by trying to better understand the impact of this disease and provide evidence on how to further integrate supportive care services throughout and after treatment.

Epidemiology of lung cancer

Lung cancer is the leading cause of cancer-related mortality in the majority of Western countries (Figure 1).[1,3] In the United States alone, approximately 235.000 new patients are diagnosed with lung cancer each year leading to over 140.000 annual deaths.[3,18] Rates across most Western European countries are similar.[1,2,19] Lung cancer is a heterogeneous disease and is classified

according to several subtypes. Approximately 95% of all lung cancer cases comprise non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC).[20] Typically, a diagnosis of NSCLC is categorized as either an adenocarcinoma or squamous cell carcinoma. Approximately 10 percent of all patients with lung cancer are diagnosed with SCLC and patients diagnosed with this subtype of lung cancer often face a very poor prognosis. The remainder comprises a heterogeneous group of thoracic cancers (e.g. mesothelioma or thymus carcinoma).

Smoking or smoke exposure is the major risk factor for the development of lung cancer and has been estimated to cause approximately 80 to 85 percent of all new cases.[21] Genetic factors have also been suggested but the cause is most probably multifactorial and clear links have yet to be elucidated.[22] Although the percentage of smokers is slowly declining in most Western countries, current predictions imply that lung cancer will likely still be a major problem well into the first half of this century.[23]

Increasingly, screening patients at risk for developing lung cancer (primarily based on their smoking history) may become a cost-effective strategy and seems promising in effectively detecting tumors in an earlier stage.[24,25] Screening is usually performed by low-dose computed tomography (CT) scanning at regular intervals in at-risk populations based on smoking history. This will likely cause a larger proportion of patients to be diagnosed with early rather than metastatic disease and thereby significantly impact the prognosis of these patients.

	Male			Female		
Estimated New Cases	Prostate	174,650	20%	Breast	268,600	30%
	Lung & bronchus	116,440	13%	Lung & bronchus	111,710	13%
	Colon & rectum	78,500	9%	Colon & rectum	67,100	7%
	Urinary bladder	61,700	7%	Uterine corpus	61,880	7%
	Melanoma of the skin	57,220	7%	Melanoma of the skin	39,260	5%
	Kidney & renal pelvis	44,120	5%	Thyroid	37,810	4%
	Non-Hodgkin lymphoma	41,090	5%	Non-Hodgkin lymphoma	33,110	4%
	Oral cavity & pharynx	38,140	4%	Kidney & renal pelvis	29,700	3%
	Leukemia	35,920	4%	Pancreas	26,830	3%
	Pancreas	29,940	3%	Leukemia	25,860	3%
	All sites	**870,970**		**All sites**	**891,480**	
	Male			**Female**		
Estimated Deaths	Lung & bronchus	76,650	24%	Lung & bronchus	66,020	23%
	Prostate	31,620	10%	Breast	41,760	15%
	Colon & rectum	27,640	9%	Colon & rectum	23,380	8%
	Pancreas	23,800	7%	Pancreas	21,950	8%
	Liver & intrahepatic bile duct	21,600	7%	Ovary	13,980	5%
	Leukemia	13,150	4%	Uterine corpus	12,160	4%
	Esophagus	13,020	4%	Liver & intrahepatic bile duct	10,180	4%
	Urinary bladder	12,870	4%	Leukemia	9,690	3%
	Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,460	3%
	Brain & other nervous system	9,910	3%	Brain & other nervous system	7,850	3%
	All sites	**321,670**		**All sites**	**285,210**	

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

FIGURE 1. Leading sites of new cancer cases and death: 2019 estimates from the American Cancer Society

All patients with suspected symptoms should be evaluated promptly yet the diagnosis of lung cancer often comes unexpected.[26] The majority of patients present to their general practitioner with vague yet persistent complaints such as a recurrent cough, hemoptysis, chest pain, recurrent signs of pneumonia, or dyspnea.[27,28] Once a diagnosis is suspected, chest imaging studies are performed as a first step, frequently followed by a histological biopsy to confirm the diagnosis and histological subtype of lung cancer. The "Tumor Node Metastasis" (TNM) classification is subsequently used to stage the disease and assess the extent of spread of the cancer throughout the body.[29] The TNM-classification, usually supplemented with a combined Positron Emission Tomography (PET)/CT scan to assess the extent of (metastatic) disease, provides a basis for a patient's prognosis and selection of a treatment modality.

A horizon of treatment modalities

A variety of treatment modalities are currently available to treat lung cancer and new pharmaceuticals and combination strategies are continuously being developed.[14] The disease stage and histological subtype, as well as a patient's comorbidities, age, and pulmonary function are usually determining factors when deciding on a treatment strategy. In addition, the Karnofsky or Eastern Cooperative Oncology Group (ECOG) performance status is used to assess a patient's functional status and better guide clinicians in their treatment recommendation.[30,31]

Despite the increased uptake of screening programs, only a minority of patients are initially diagnosed with localized disease.[18,32] Fortunately, those patients diagnosed can often still be treated curatively through radical local treatment via surgical resection or stereotactic radiotherapy, sometimes preceded or followed by chemotherapy. For those patients diagnosed with locally advanced or unresectable lung cancer, concurrent chemoradiation therapy, possibly followed by immunotherapy, is a viable treatment option.[33]

In contrast, the majority of patients are diagnosed with metastasized disease. These patients are often treated with a systemic form of treatment such as platinum-based chemotherapeutic agents, medication targeting specific mutations, immunotherapy, or a combination of these agents. Molecular tumor characterization has become an important routine part of the diagnostic process for these patients since several mutations, also referred to as proto-oncogenes or driver mutations, often spur the proliferation of malignant cells.[34] Molecular characterization is usually achieved through the use of histological biopsies but this is an invasive and potentially time-consuming procedure. Instead, liquid biopsies using circulating tumor material from a patient's blood to characterize the tumor are increasingly propagated as a feasible and less invasive alternative.[35] Examples of important mutations include the Epidermal Growth Factor Receptor (EGFR), the BRAF V600E, and the Anaplastic Lymphoma Kinase

(ALK) translocation.[36] The outcome of this characterization provides clinicians as well as patients with an increasingly complex array of different treatment options and is often linked to a patient's prognosis.[34]

Immunotherapy

In recent years, several landmark studies have provided clear evidence for a markedly prolonged tumor response among patients with different types of lung cancer treated with immunotherapy.[13,37–39] Consequently, immunotherapy, provided as monotherapy or in combination with chemotherapy, is now the recommended first-line therapy among specific subgroups of patients with NSCLC.[40] This class of drugs works primarily on Programmed Cell Death Protein (PD-1) and effectively binds the PD-1 receptor of lymphocytes thereby blocking the signaling proteins that allow cancerous cells to hide from the body's immune system. Currently, pembrolizumab, nivolumab, atezolizumab and durvalumab are the registered immunotherapy agents available to treat patients. New drug combinations are continuously being developed, tested and combined with existing treatments.

The development of this exciting new treatment modality has markedly improved the prognosis of selected patients with advanced stage lung cancer (so-called responders).[33,41] Yet, despite clear average survival benefits, this form of treatment does not work for all patients and there are still many unknowns especially with regards to costs, optimal selection of eligible patients, and timely recognition and treatment of possibly harmful side-effects that may severely impact QoL.[42] Ensuring the continuous delivery of high-quality care aligned with patient's personal preferences therefore remains an important challenge in this era of immunotherapy and other treatment advances. Further, the development of high-quality survivorship care to better address the needs of those patients living longer with or beyond (metastatic) lung cancer is becoming ever more relevant.

The impact of a diagnosis

After a histological confirmation of the diagnosis and multi-disciplinary development of a treatment plan, patients and their caregivers are scheduled to have a conversation with their oncologist to discuss treatment options and a subsequent treatment plan. The majority of patients are diagnosed with advanced stage lung cancer thereby making curative treatment no longer an option.[1] Throughout treatment, distressing side-effects of treatment, especially from chemotherapeutic agents or immunotherapy, may cause debilitating symptoms that can or may not always treated.[4,43] Patients and their caregivers therefore face difficult and preference-sensitive treatment trade-offs on whether to pursue treatment or primarily focus on symptom relief. Particularly for patients diagnosed with SCLC, it is important to realize that

symptoms can also be alleviated through treatment with chemotherapy. Whether or not to pursue treatment is therefore an increasingly difficult choice for patients as well as the treating pulmonary oncologist.

In contrast to patients with other cancers, research has shown that patients with lung cancer are more distressed and experience a higher symptom burden throughout and after treatment.[44,45] In part, this may be explained by the relatively high burden of comorbidities as well as to stigma associated with the disease.[46–48] Such factors negatively affect the QoL that many patients experience throughout and after treatment. In addition, the prognosis for most patients with advanced or metastatic lung cancer, despite the recent treatment advances, is still poor with a 5-year survival rate approximating 10 percent.[18] Early and routine integration of supportive care is therefore particularly important to enable patient-centered conversations earlier in the disease course and prevent the overuse of aggressive therapies (e.g. chemotherapy) very near to the end of life.[49–53] Ultimately, these conversations and services should lead to care concordant with patient's preferences and improved well-being.[54–57]

Integrated palliative and supportive care

As displayed in Figure 2, the traditional model of supportive care and care near the end of life clearly distinguishes curative treatment from supportive or palliative treatment. Lynn et al.[58] argued in 2003 that such care should preferably be delivered earlier, conjointly with cancer or disease modifying therapy, and continue for patients living with a chronic serious illness or after a patient's death (bereavement care).[16,59] In the setting of pulmonary oncology, the landmark study first providing clear evidence to support this model was conducted by Temel et al.[60] A total of 151 patients with advanced stage NSCLC were randomized to receive either early and integrated palliative care or care as usual. After a 12 week follow-up, the researchers observed marked improvements in QoL, mood, aggressiveness of end-of-life care and even survival. Since then, several studies across different settings and populations have provided similar findings.[61–65]

Although this growing body of evidence is increasingly endorsed by various international guidelines,[16,66] integration and translation of these services in clinical practice still lacks. Studies have shown that this delay may lead to poor quality care,[43,67] an overuse of aggressive therapies near to the end of life,[10,51,68] and increased levels of distress among patients and caregivers.[69] Clinicians often fear that "transitioning" to palliative/supportive care might take away hope or be distressing to patients.[9,70] Previous research, however, demonstrated that earlier and better conversations about topics such as prognosis may actually improve the patient-clinician relationship, positively impact QoL, and possibly even help patients live longer.[65,71] Strategies to better embed this line of care across different settings and in an earlier stage are therefore urgently needed.

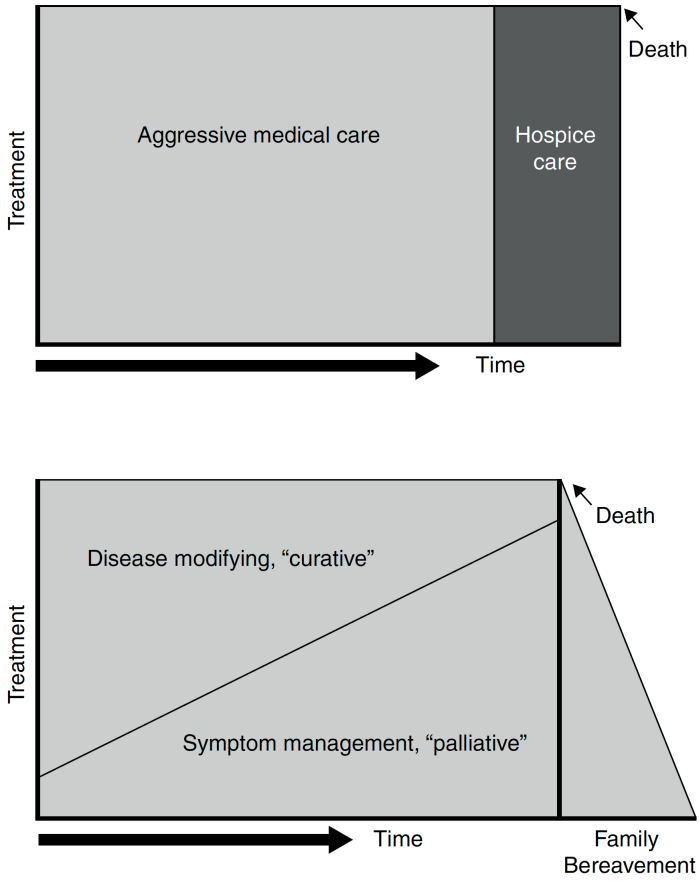

FIGURE 2. Model by Lynn and Adamson with the traditional concept of appropriate care near the end of life and the new concept as presented in 2003.

OUTLINE OF THIS THESIS

The overall aim of this thesis is to improve our understanding of the impact of lung cancer and provide evidence on how to integrate high quality, patient-centered supportive care. Studies included in this thesis are based on quantitative as well as qualitative methodologies. Additionally, a systematic literature review and a commentary paper are included as separate chapters. The outline and corresponding research objectives are as follows:

In **chapter 2,** a systematic review is presented on the effects of interventions facilitating shared-decision making among patients with lung cancer. We specifically report on the effects on

distress and healthcare utilization. In **chapter 3,** a randomized controlled trial conducted among patients with lung cancer is reported. This trial evaluated the effects of a novel approach to screen for distress and additional supportive care on QoL, mood, and end-of-life care using the Distress Thermometer (DT) and the associated Problem List. In **chapter 4**, we subsequently study the added prognostic value of a patient-centered outcome, the DT-score, in assessing one-year survival. We used data obtained from the randomized controlled trial.

The subsequent chapters focus on a mixed population of patients with advanced cancer (including lung cancer) and on cancer survivorship. **Chapter 5** outlines a qualitative study based on advance care planning (ACP) conversations between clinicians using a structured and evidence-based conversation guide and patients with advanced cancer. Our aim was to characterize these conversations and identify opportunities for improvements. In **chapter 6,** we proceeded to study the concordance of these audio-recorded conversations with available clinician documentation. Our goal was to examine the extent to which the documentation of serious illness communication reflects the content and nuances of ACP conversations, particularly with regards to patients' stated preferences or concerns. These data were obtained from a cluster randomized controlled trial of which the outcomes are outlined in **appendix I.**

Chapter 7 functions as a transitionary chapter and describes the progress and challenges for both survivorship and palliative care among patients living with or beyond advanced cancer. In line with this chapter, we developed and validated the "Cancer Survivor Core Set" detailing on the most relevant health-related problems as faced by survivors of cancer in **chapter 8.**

Last, **chapter 9** serves as the general discussion of this thesis. We will first summarize our main findings, provide a critical appraisal contrasted to recent literature, outline methodological challenges and present implications the implications of our findings.

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II

Chapter 2

Effects of shared decision making on distress and healthcare utilization among patients with lung cancer: A systematic review

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ABSTRACT

Context: Lung cancer is associated with significant distress, poor quality of life, and a median prognosis of less than one year. Benefits of shared decision making (SDM) have been described for multiple diseases, either by the use of decisions aids or as part of supportive care interventions.

Objectives: To summarize the effects of interventions facilitating SDM on distress and healthcare utilization among patients with lung cancer.

Methods: We performed a systematic literature search in the CINAHL, Cochrane, EMBASE, MEDLINE, and PsychINFO databases. Studies were eligible when conducted in a population of patients with lung cancer, evaluated the effects of an intervention that facilitated SDM, and measured distress and/or health care utilization as outcomes.

Results: A total of 12 studies, detailed in 13 publications, were included: nine randomized trials and three retrospective cohort studies. All studies reported on a supportive care intervention facilitating SDM as part of their intervention. Eight studies described effects on distress and eight studies measured effects on healthcare utilization. No effect was found in studies measuring generic distress. Positive effects, in favor of the intervention groups, were observed in studies using anxiety-specific measures (n=1) or depression-specific measures (n=3). Evidence for reductions in healthcare utilization was found in five studies.

Conclusion: Although not supported by all studies, our findings suggest that facilitating SDM in the context of lung cancer may lead to improved emotional outcomes and less aggressive therapies. Future studies, explicitly studying the effects of SDM by using decision aids, are needed to better elucidate potential benefits.

INTRODUCTION

Lung cancer represents 13% of all cancer diagnoses and remains one of the most frequently diagnosed cancers worldwide. It is the leading cause of cancer deaths with a median prognosis of less than one year.[1] Patients with lung cancer experience high levels of distress throughout and after treatment, especially when compared to patients with other types of cancer.[2,3] Also, the overuse of aggressive therapies (e.g. chemotherapy) near the end of life is increasingly regarded as disadvantageous.[4–7] Patient-centred conversations earlier in the disease course may lead to improved emotional well-being and to care that is aligned with patients' personal preferences.[8,9]

To better achieve such conversations, especially when patients are faced with difficult treatment trade-offs, an increased emphasis is put on the concept of shared decision making (SDM).[10,11] Especially in preference-sensitive decisions, such as the decision on whether or not to pursue a new course of treatment when faced with a life-limiting illness, SDM is of critical relevance.[10,12–15] To date however, patient values and personal preferences are not routinely integrated in clinical care mainly due to time constraints, unawareness, or uncertainty on part of the clinician.[13,16,17] In contrast to this, a majority of patients do express a desire to have a role in SDM, emphasizing the need to further develop evidence on how to facilitate such a process.[18–23]

Facilitation of SDM has been shown to improve a patients' emotional state of well-being, increase patient or caregiver involvement, increase decision satisfaction, and possibly reduce overly aggressive therapies near the end of life.[24,25] In other settings, tools have been developed to specifically facilitate SDM in clinical practice.[26,27] Such tools, hereafter referred to as decision aids, usually inform patients about benefits and disadvantages of different (treatment) alternatives. To date however, no study has summarized the effects of SDM in patients with lung cancer. We therefore conducted a systematic review to summarize the available evidence on the effects of SDM in patients with lung cancer and focused on the effects on distress and healthcare utilization.

METHODS

Design and data sources

The review protocol was registered in PROSPERO (CRD42015026954). We systematically searched the CINAHL, Cochrane, EMBASE, MEDLINE, and PsychINFO databases. Two search updates were performed; the latest update was conducted on 2 May 2018. Terms used in our electronic search strategy were shared decision-making, lung cancer, distress and healthcare utilization. We decided to use a broad search strategy since no MESH heading for "shared decision making" is available. This search strategy included both subject headings and free text terms and was adjusted for the use of synonyms and alternative spellings (Supplement A). A librarian assisted this process. All references were exported to RefWorks, ProQuest LCC, 2017 and duplicates were removed. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist throughout the reporting of our study.[28]

Eligible studies

Two investigators (MES and OPG) independently performed an initial screening based on title and abstract. The same investigators performed a full-text appraisal of the remaining studies to determine final inclusion. Reference lists of all included studies were hand searched for additional studies. Disagreements were resolved through a consensus discussion with a third independent investigator (AJB). Studies were eligible for inclusion if all of the following criteria were met:

1. The study contained original data;
2. The study included 100 patients with a confirmed diagnosis of lung cancer; authors of studies which included a sample of different cancer populations without reporting separately on the subsample of lung cancer patients were approached for data on the lung cancer patients;
3. The study explicitly detailed on the facilitation of SDM, either as part of a supportive care intervention or by use of a decision aid;
4. SDM had to be facilitated throughout treatment-related decisions: studies reporting on decision rules for clinicians, decisions on lifestyle changes only, clinical trial entry, or education programs not geared towards a specific decision were excluded;
5. The study had a control group in which patients received usual care, we accepted both randomized and non-randomized studies;
6. At least one outcome measure of distress and/or healthcare utilization was used.

We used the definition as provided by Towle et al.[11] to delineate SDM: A process to make decisions that are shared by both doctor and patient by informing patients using best evidence

about risks and benefits including patient-specific characteristics and values. Distress was defined as: "emotional and/or physical distress measured by a generic distress scale and/or a scale measuring symptoms of depression or anxiety".[29] Questionnaires measuring distress were considered to quantify generic distress if two or more of the following domains were covered: physical problems, spiritual problems, social problems, or symptoms of anxiety or depression. We defined healthcare utilization as "any measure quantifying the amount of care a patient may have received" (e.g. the number of hospitalizations throughout the study period or whether a patient received chemotherapy in the last 30 days of life). The time period as defined by the study was used. Since healthcare utilization may be expressed in many different ways, we decided to summarize the effects on the three most frequently used outcomes of healthcare utilization across all included studies. All other outcomes and results related to healthcare utilization are provided in Supplement B.

Data extraction and statistical analysis

A standardized data extraction form following the CONSORT criteria[30,31] was developed to synthesize the data of selected studies. The extraction form consisted of nine items assessing study methodology (e.g. study design and the follow-up period) and six items evaluating the study's results (e.g. flow of participants throughout the study and numbers of participants analyzed). Whenever multiple measures of one outcome (e.g. different questionnaires to quantify distress) were used, we extracted data from all measures. Different publications detailing on the same study population were analyzed as one study. We expected that pooling of results in a meta-analysis would not be feasible due to intervention- and outcome measures heterogeneity. When the number of studies included was considered too small to perform subgroup analyses, the 'best evidence' approach was performed including an analysis of the strength of evidence.[32]

Clinical relevance was assessed based on available literature regarding the "Minimally Clinical Important Difference" (MCID). The following MCID's and cutoff scores were used: +3 for the Edmonton Symptom Assessment System (ESAS),[33,34] +1.5 for the Hospital Anxiety and Depression Scale (HADS) or a subscale cutoff of >7 with a minimal 5% difference between study groups,[35] a cutoff of >4 for the Brief Distress Thermometer (BDT) with a minimal 5% difference between study groups,[36] and a minimal change of 50% from baseline score for the Patient Health Questionnaire-9.[37] An MCID or cutoff score for the Symptom Distress Scale (SDS) was not found. Therefore, we applied the rule of half a standard deviation[38,39] as a best proxy leading to an estimated MCID of +3.5.[40]

Risk of bias assessment

The Cochrane Collaborations' Risk of bias tool was used to assess risk of bias.[41] Using this tool, seven aspects that may be subject to bias were assessed: 1) random sequence generation, allocation concealment, 3) blinding of participants or personnel, 4) blinding of outcome assessors, 5) incomplete outcome data, 6) selective outcome reporting, and 7) other potential sources of bias including unbalanced groups at baseline. This tool is primarily designed to assess risk of bias in RCTs. For uniformity, we decided to also use this tool in other studies and score RCT-specific aspects as non-applicable.

Risk of bias of included studies was assessed and reported in a standardized spreadsheet by two independent investigators (MES and OPG or MES and AJB). For each category, the risk of bias was assessed as low, high, or unclear. Discrepancies were resolved by consensus and settled through discussion with a third independent investigator (AJB or MYB).

RESULTS

Search results

The search yielded 4929 titles and was reduced to 3633 titles after removing duplicates. Of these, 92 titles met the criteria for a full text review. A total of 12 eligible studies, reported in 13 publications, were included: nine randomized controlled trials (RCTs) and three retrospective cohort studies (Figure 1).[25,42–53] Three of the RCTs were performed in mixed cancer populations.[42,46,53] Comparison of the subsamples of patients with lung cancer vs. the total study samples showed that patients with lung cancer suffered from more distress when compared to the total sample (data not shown). Pooling of results in a meta-analysis was not performed due to intervention- and outcome measures heterogeneity.

Description of interventions

All included studies detailed on a supportive care intervention facilitating SDM as part of the intervention. None of the included studies described the effects of a decision aid. Overall, the goal of such multi-component interventions was to provide earlier and systematic access to palliative care services through either specially trained advanced practice nurses, a registered nurse case manager, or members of a palliative care team. Interventions were primarily aimed at improving emotional well-being and QoL by encouraging self-management, addressing symptom burden, and discussing unmet needs. Table 1 provides further details on the characteristics of the included studies (13 publications). For clarity, all tables are included at the end of the report.

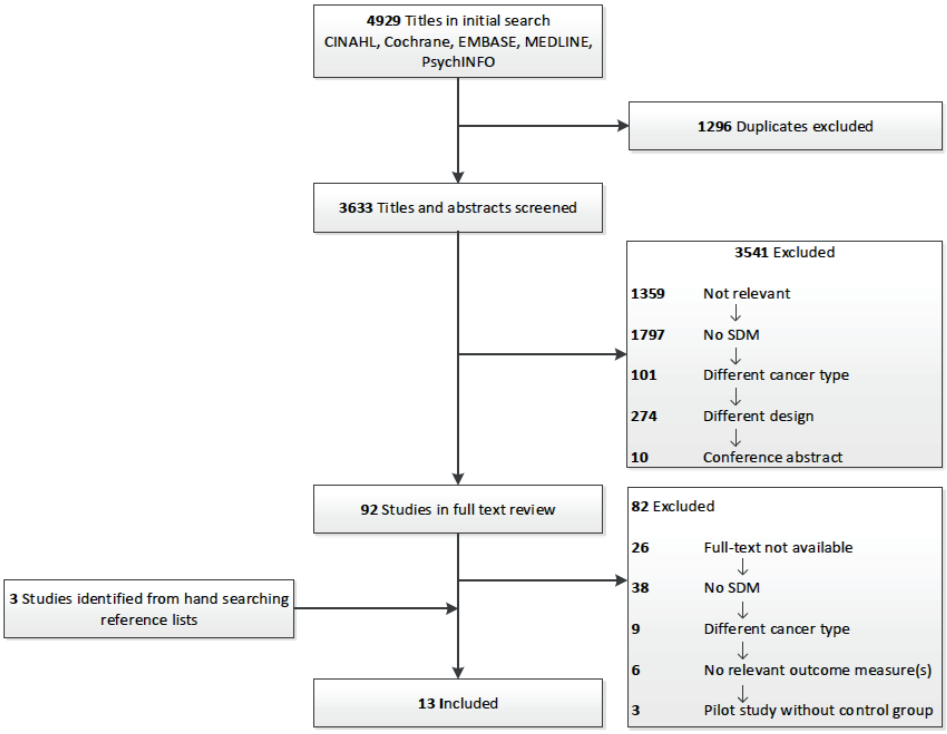

FIGURE 1. Flow chart reporting on selection of articles based on the Flow Diagram by the PRISMA Statement

Measures of distress

Effects on distress are summarized in Table 2 and the data below are displayed as intervention group (group for which SDM was facilitated) vs. control group. Eight RCTs, comprising 1294 patients with lung cancer, evaluated effects on distress.[25,42,47,49–53] Five studies measured generic distress using either the ESAS,[42,53] the HADS total score, [47,50] the BDT,[50] or the SDS.[51] Four studies measured anxiety, all using the HADS-A subscale.[25,47,49,52] Five studies measured depression and used either the Center for Epidemiologic studies Depression Scale (CES-D),[42] the Patient Health Questionnaire (PHQ-9),[25,49,52] or the HADS-D subscale.[25,47,49,52] Only statistically significant differences are detailed below. Based on the previously described MCID's, clinically relevant differences are displayed in Table 2.

TABLE 1. Characteristics of included studies

Source	Study design	Study population	Setting	Follow-up	SDM intervention	Control group	Primary outcome(s)
Bakitas et al. (2009)[a]	RCT	117 patients with advanced lung cancer	Dartmouth-Hitchcock Norris Cotton Cancer Center, affiliated outreach clinics and VA Medical Center Various locations, New Hampshire and Vermont, USA	13 months or until death	Telephone based case management, educational approach to encourage patient activation, self- management, and empowerment	Allowed to use all oncology and supportive services without restriction	Quality of life: FACT-L Symptom intensity: ESAS Resource use
Basch et al. (2016)[a]	RCT	201 patients starting with chemotherapy for metastatic lung cancer	Memorial Sloan Kettering Cancer Center New York City, New York, USA	Median 3 months (range: 0.25 to 49 months)	Web-based self-report of symptom burden, email alerts to nurses, symptom report printed at each clinical visit for both nurse and oncologist.	Standard procedure for monitoring and documenting symptoms: discussed and documented in the medical record during clinical encounters between patients and oncologists	Health related quality of life: EuroQoL EQ-5D
Geerse et al. (2016)	RCT	223 patients with newly diagnosed or recurrent lung cancer starting systemic therapy	University Medical Center Groningen Groningen, Groningen, The Netherlands	25 weeks	Distress thermometer and problem list before outpatient visit, followed by face-to-face meeting with psychosocial nurse and referral if appropriate	Medical and psychosocial care as offered by treating physician every 3 weeks	Quality of life: EORTC-QLQ-C30
Temel et al. (2010) and Greer et al. (2012)	RCT	151 patients with newly diagnosed, metastatic non-small cell lung cancer	Massachusetts General Hospital Boston, Massachusetts, USA	12 weeks 18 months	Attention to physical and psychosocial symptoms, establishing goals of care, assisting with decision making regarding treatment, coordinating care	Not scheduled to meet with the palliative care service unless a meeting was requested by the patient, the family, or the oncologist	Quality of life: Trial Outcome Index
Temel et al. (2017)[a]	RCT	191 patients with newly diagnoses incurable lung cancer	Massachusetts General Hospital Boston, Massachusetts, USA	12 weeks and 24 weeks	Outpatient palliative care at visit at least once a month	Usual oncology care, able to meet PC clinician only upon request.	Quality of life: FACT-G after 12 weeks
Schofield et al. (2013)	RCT	108 patients with inoperable lung or pleural cancer	Peter MacCallum Cancer Center, Melbourne, Victoria, Australia	12 weeks	Meeting individualized unmet needs of patients by providing information and support	Standard care as per hospital protocol for Advanced Lung Cancer Patients	Unmet needs: Needs Assessment

TABLE 1. Continued

Source	Study design	Study population	Setting	Follow-up	SDM intervention	Control group	Primary outcome(s)
Yount et al. (2014)	RCT	253 patients with stage III or IV non-small cell lung cancer or small-cell lung cancer	Northwestern University, Rush University Medical Center, John. H. Stroger Jr. Hospital Chicago, Illinois, USA	12 weeks	Weekly monitoring of symptoms with reporting to the clinical team	Weekly symptom monitoring alone Distress Scale	Overall symptom burden: Symptom
Zhuang et al. (2018)	RCT	150 patients with diagnosed non-small cell lung cancer	First People's Hospital of Xianyang City Xi'An, Shaanxi, China	12 weeks	Early palliative care by board-certified palliative care physicians and advanced-practice nurses	Treated only with conventional tumor management	Not specified
Zimmermann et al. (2014)[a]	Cluster-RCT	101 patients with advanced lung cancer	Princess Margaret Cancer Center Toronto, Ontario, Canada	4 months	(1) Multidisciplinary assessment of symptoms, distress, and support (2) Telephone contact with palliative care nurse (3) Palliative care follow-up (4) A 24 on-call telephone service	No formal intervention, but palliative care referral was not denied, if requested	Quality of life: FACIT-Sp
King et al. (2016)	Retrospective cohort study	207 patients with advanced lung cancer	Carbone Cancer Center Madison, Wisconsin, USA	-	Early palliative care provided by one oncologist	Standard oncology care by any other oncologist	Survival
Nieder et al. (2016)[b]	Retrospective cohort study	286 patients with histologically confirmed non-small cell lung cancer	Nordland Hospital Trust Bodo Center Bodo, Salten, Norway	-	Received either **early** or **late** palliative care throughout the study period	Did not receive palliative care, standard oncology care	Not specified
Reville et al. (2010)	Retrospective cohort study	1476 patients with primary or secondary diagnosis of lung cancer	Thomas Jefferson University Hospital Philadelphia, Pennsylvania, USA	-	Received a palliative care consultation	Did not receive a palliative care consultation	Not specified

Abbreviations: FACT-G Functional Assessment of Cancer Therapy-General. FACT-L: Functional Assessment of Cancer Therapy-Lung cancer. FACIT-Sp: Functional Assessment of Chronic Illness Therapy - Spiritual Well-Being. ESAS: Edmonton symptom assessment system. EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 36. RCT: randomized controlled trial.

[a] The complete study included a larger sample of patients with different types of cancer. Data of the subsample of patients with lung cancer is displayed in this table

[b] Data were analyzed and displayed as three groups: early palliative care (>3 months before death), late palliative care (<3 months before death), or no palliative care

TABLE 2. Effect of included studies on general distress measures, anxiety-specific measures, and depression-specific measures

Source	General distress	Anxiety	Depression
Bakitas et al. (2009)[a]	ESAS linear mixed model analysis p=0.72 ESAS mean score after 4 months 3.16 vs. 2.80, p=0.49	-	CES-D Linear mixed model analysis p=0.39 CES-D mean score after 4 months 11.1 vs. 11.6 p=0.92
Geerse et al. (2016)	HADS-Total mean change score at 25 weeks -2.1 vs. -2.4, p=0.85	HADS-A mean change score at 25 weeks -1.3 vs. -1.3, p=0.98	HADS-D mean change score at 25 weeks -0.6 vs. -0.9, p=0.77
Temel et al. (2010)	-	HADS-A percentage above cutoff score at 12 weeks 25% vs. 30%[c], p=0.66	HADS-D percentage above cutoff score at 12 weeks 16% vs. 38%[c], p<0.01 PHQ-9 percentage above cutoff score at 12 weeks 4% vs. 17%[c], p=0.04
Temel et al. (2017)[a]	-	HADS-A mean score after 12 weeks 4.47 vs. 5.23[b] HADS-A mean score after 24 weeks 4.63 vs. 5.24[b]	PHQ-9 adjusted mean score at 12 weeks 5.61 vs. 7.21, p=0.04 PHQ-9 adjusted mean score at 24 weeks 5.54 vs. 6.71, p=0.05 HADS-D mean score after 12 weeks 4.90 vs. 5.26[b] HADS-D mean score after 24 weeks 4.44 vs. 5.03[b]
Schofield et al. (2013)	HADS-total mean score 12 weeks post-treatment 11.52 vs. 10.34, p=0.48 BDT mean score 12 weeks post-treatment 2. 85 vs. 2.99, p=0.81	-	-
Yount et al. (2014)	SDS mean score at 12 weeks adjusted for baseline 25.3 vs. 25.5, p=0.51	-	-

TABLE 2. Continued

Source	General distress	Anxiety	Depression
Zhuang et al. (2018)	-	HADS-A percentage above cutoff at 12 weeks 17% vs. 27%[c], p<0.05	HADS-D percentage above cutoff at 12 weeks 19% vs. 32%[c], p<0.001 PHQ-9 percentage above cutoff at 12 weeks 9% vs. 16%[c], p<0.001
Zimmermann et al. (2014)[a]	ESAS change from baseline score 3 months: -0.62 vs. 0.42, adjusted difference 1.01, p=0.81 ESAS change from baseline score 4 months: -1.97 vs. 0.91, adjusted difference 3.67[c], p=0.38	-	-

Data on group for which SDM was facilitated vs. control group are displayed. Abbreviations: BDT: Brief Distress Thermometer. CES-D: Center for Epidemiological Studies Depression Scale. ESAS: Edmonton Symptom Assessment Scale. HADS-A: Hospital Anxiety and Depression Scale – Anxiety. HADS-D: Hospital Anxiety and Depression Scale – Depression. PHQ-9: Patient Health Questionnaire. SDS: Symptom Distress Scale

a The complete study included a larger sample of patients with different types of cancer. Data of the subsample of patients with lung cancer is displayed in this table.

b No p-value provided, but according to authors no significant difference

c Clinically relevant outcome.

Effects on distress

Generic distress

None of the five studies measuring generic distress showed statistically significant differences between the intervention group and the usual care group at any time point.[42,47,50,51,53]

Anxiety

Of the four studies measuring anxiety, one study (n=150) showed a significantly lower percentage of patients with symptoms of anxiety after 12 weeks in the intervention group (17% vs. 27%; p<0.05).[52] Another study (n=151) showed the same trend but there was no significant difference (25% vs. 30%; p=0.66).[25] The other two studies showed no significant differences in mean anxiety scores.[47,49]

Depression

Three out of five studies measuring depression observed beneficial effects favoring the intervention group. Two studies (n=151 and n=150) showed a significantly lower proportion of patients with high levels of depression as measured with the HADS-D (16% vs. 38%; p<0.001 and 19% vs. 32%; p<0.001, respectively).[25,52] These two studies found similar effects in the PHQ-9 scores (data not shown) as did the third study (n=191): mean depression scores on the PHQ-9 at both 12 weeks (5.61 vs. 7.21; p=0.04) and 24 weeks (5.54 vs. 6.71; p=0.05).[49] The latter study showed no effect in the HADS-D.[49] The two other studies compared mean depression scores and observed no significant differences.[42,47]

Measures of healthcare utilization

Effects on healthcare utilization are summarized in Table 3 and the data below are displayed as intervention group (group for which SDM was facilitated) vs. control group. Eight studies, reported in nine publications and detailing on data from 2914 patients, described effects on healthcare utilization: five RCT's[25,42,46–48,51] and three retrospective cohort studies.[43–45] Across these studies, effects on hospitalizations (n=7),[25,42,44,46–48,51] emergency department (ED)-visits (n=5),[25,42,46–48,51] and the use of chemotherapy (n=5)[25,43,44,46–48] were the three most frequently used outcomes and are summarized in detail below. All other outcomes and results related to healthcare utilization are provided in Supplement B.

Hospitalizations

Two of the retrospective studies found evidence for changes with regard to hospitalizations. One of these studies (n=286) compared the percentage of patients that were hospitalized in the last three months before death, across patients receiving early palliative care, late palliative care, or no palliative care (73% vs. 97% vs. 88%; p=0.03).[44] The other study (n=1476) observed that patients who had received a palliative care consultation had a longer mean length of stay (16.3

days vs. 8.3 days; p<0.001).[45] The five RCTs detailing on this showed no significant differences for hospitalizations between intervention and control group.[25,42,46,48,51] In two of these studies (n=151 and n=223), a trend towards significance, favoring the intervention groups, was observed in the percentage of hospitalized patients in the last 30 days of life: 37% vs. 54%; no p-value provided, and 47% vs. 56%; p=0.23.[25,47]

Emergency department visits

One RCT (n=201) found that the cumulative incidence of patients admitted to the ED was lower in the intervention group (39% vs. 53%; p=0.02).[46] Similar trends, although not significant, were observed in two other RCTs (ED-visits in last 30 days of life: 22% vs. 30%; no p-value provided, and 25% vs. 38%; p=0.09).[25,47] The remaining two studies did not find differences between the mean number of ED-visits in both study groups.[42,51]

Use of chemotherapy

One RCT (n=223) and one retrospective cohort study (n=286, analyzing early palliative care vs. late palliative care vs. no palliative care) reported a significantly lower proportion of patients in the intervention group who received chemotherapy in the last 30 days of life: 12% vs. 26%; p=0.03 and 14% vs. 40% vs. 28%; p=0.003, respectively.[44,47] Another RCT (n=151) found similar effects when analyzing the use of chemotherapy in the last 60 days of life (53% vs. 70%; p=0.05) and a trend in the last 30 days of life 30% vs 43%; p=0.14.[25,48] The other two studies did not observe significant differences in the use of chemotherapy, either as measured by the mean duration of chemotherapy or by the number of chemotherapy treatments.[43,46]

Risk of bias

Assessment of the risk of bias of individual studies is shown in Figure 2. Overall, the risk of selection bias and attrition bias was perceived as low in most RCT's. A high risk of bias was found regarding blinding of participants or personnel, which was not performed in most studies due to the nature of the interventions. Reporting bias was unclear in some studies since not all study protocols were made publicly available online prior to publication. In two retrospective studies, the study groups were not comparable thereby making selection bias highly likely.[44,45] In the third retrospective study this was unclear due to scarce information.[43]

TABLE 3. Effects on hospitalizations, emergency department visits, and use of chemotherapy

Source	Hospitalizations	Emergency department visits	Use of chemotherapy
Bakitas et al. (2009)[a]	Number of days in hospital between randomization and reference date[c] 3.1 days vs. 2.2 days, p=0.66	Mean number of ED visits between randomization and reference date[c] 0.5 vs. 0.4, p=0.81	-
Basch et al. (2016)[a]	Hospitalizations (cumulative incidence at one year) 52% vs. 56% p=0.40	ED visits (cumulative incidence at one year) 39% vs. 53%, p=0.02	Mean duration of chemotherapy 7.49 vs. 5.64 months vs 7.49, p=0.10 Median duration of chemotherapy 3.47 vs. 2.76 months, p=0.35
Geerse et al. (2016)	Hospitalizations between randomization and death: 73% vs. 76%, p=0.61 Hospitalizations in last 14 days of life 33% vs. 43%, p=0.22 Hospitalizations in last 30 days of life 47% vs. 56%, p=0.23	ED visit(s) between randomization and death 58% vs. 69%, p=0.15 ED visit(s) in last 14 days of life 18% vs. 25%, p=0.28 ED visit(s) in last 30 days of life 25% vs. 38%, p=0.09	Chemotherapy in last 14 days of life 4% vs. 11%, p=0.10 Chemotherapy in last 30 days 12% vs. 26%, p=0.03
King et al. (2016)	-	-	Chemotherapy ≥ 2 lines 48% vs. 52%, adjusted OR 1.12, p=0.71 Chemotherapy in last 14 days of life 4% vs 4%, adjusted OR 0.94, p=0.93 Chemotherapy in last 30 days of life 11% vs. 17%, adjusted OR 0.66, p=0.38
Nieder et al. (2016)[c]	Hospitalized in the last 3 months of life 73% vs. 97% vs. 88%, p=0.03	-	Receipt of active anticancer treatment in the last month of life 14% vs. 40% vs. 28%, p=0.003
Reville et al. (2010)	Mean length of stay: 16.3 days vs. 8.3 days, p<0.001 Median length of stay 12.5 days vs. 6 days§	-	-

TABLE 3. Continued

Source	Hospitalizations	Emergency department visits	Use of chemotherapy
Temel et al. (2010) and Greer et al. (2012)[b]	Hospitalizations between randomization and death 74% vs. 77%[d] Hospitalizations in last 30 days of life 37% vs. 54%[d] Median length of hospitalization between randomization and death 5.0 days (range 0-50) vs. 7.0 days (range 0-45)[d]	ED visit(s) between randomization and death 53% vs. 57%[d] ED visit(s) in last 30 days of life 22% vs. 30%[d]	Chemotherapy in last 14 days of life 14% vs. 24%, p=0.18 Chemotherapy in last 30 days of life 30% vs. 43%, p=0.14 Chemotherapy in last 60 days of life 53% vs. 70%, p=0.05, adjusted OR 0.47 (0.23-0.99), p=0.05 Percentage of participants with a certain number of chemotherapy lines No chemotherapy 8% vs. 4%, p=0.49; One line 28% vs. 37%, p=0.30; Two lines 28% vs. 30%, p=0.86; Three lines 18% vs. 16%, p=0.83; Four or more lines 16% vs. 12%, p=0.64
Yount et al. (2014)	Mean number of hospital admissions during 12 weeks: 0.62 vs. 0.67, p=0.88	Mean number of ED visits during 12 weeks 0.69 vs. 0.58 , p=0.85	-

Data on group for which SDM was facilitated vs. control group are displayed. Abbreviations: ED: Emergency Department. OR: Odds Ratio, provided with 97% confidence interval.
a The complete study included a larger sample of patients with different types of cancer. Data of the subsample of patients with lung cancer is displayed in this table.
b Data were analyzed and displayed as three groups: early palliative care
(>3 months before death), late palliative care
(<3 months before death), or no palliative care
c Inclusion period: between November 2003 and May 2007. Reference date May 1, 2018.
d No p-value provided.

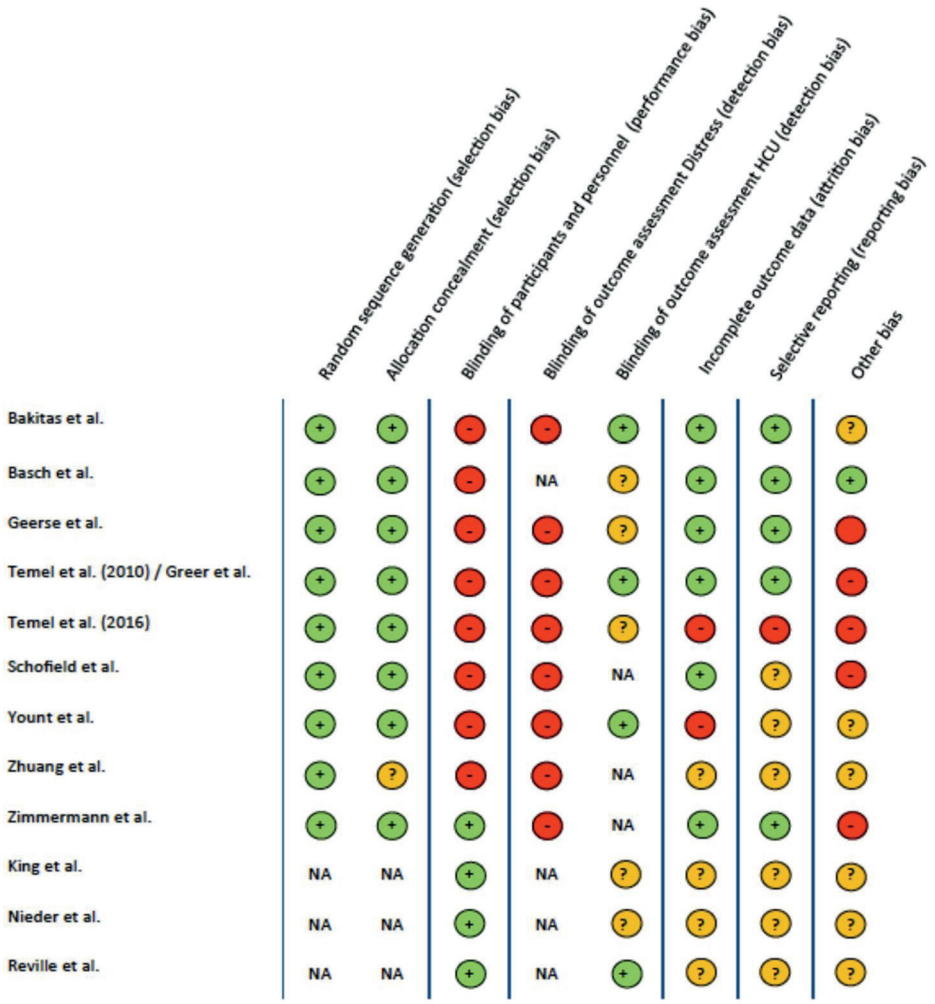

FIGURE 2. Risk of bias assessment**.** Other bias included design specific bias, baseline imbalances, differential diagnostic activity and contamination.

DISCUSSION

To our knowledge, this is the first systematic review synthesizing evidence on the effects of SDM on distress and healthcare utilization in patients with lung cancer. We identified 12 studies, detailed in 13 publications, describing the effects of supportive care interventions that facilitated SDM as part of their intervention. We found no statistically significant differences in distress in studies using a generic measure. However, mixed effects, in favor of patients for

which SDM was facilitated, were found in studies specifically measuring depression or anxiety. Regarding reductions in healthcare utilization, we observed some evidence that SDM leads to reductions in healthcare use.

A number of observations are of importance. As the incorporation of SDM is increasingly propagated for different diseases in order to truly provide patient-centered care,[54–56] we found evidence that it may lead to less depression and anxiety and reductions in healthcare use. This suggests that involving patients in treatment decisions earlier in the disease course may lead to care that is better aligned with patients' personal preferences and consequently to improved patient-reported outcomes. Yet, since all included studies described multicomponent supportive care interventions, we are not able to deduce whether SDM or other components of these interventions (e.g. earlier referrals or improved symptom management) account for the observed effects. Clearly, palliative care may also improve outcomes related to distress and healthcare utilization without the explicit facilitation of SDM. This is especially relevant since we were unable to measure exactly how and, more importantly, to what extent SDM was provided throughout the included studies.

Unfortunately, we did not identify any studies solely describing the effects of the use of a decision aid for patients with lung cancer. Several relevant pilot studies described the design and pilot testing of such tools.[57–60] These studies all conclude that facilitating SDM in clinical practice is feasible. Moreover, two of these studies provided preliminary evidence for reductions in distress, enhanced patient satisfaction, better symptom control, and improved disease knowledge and understanding.[59,60] Such tools have yet to be tested in larger cohorts of patients with (lung) cancer.

We found several research protocols describing interventions aimed at testing the effects of decision aids in patients with different types of (advanced) cancer.[61–64] Additionally, two recent systematic reviews concluded that the evidence base for SDM is at a relatively early stage.[26,27] These studies summarized the use of decision aids for patients facing health treatment or screening decisions[26] and patients with a life-limiting illness.[27] Both reviews do provide strong evidence on improved health-literacy and some evidence for reductions in decisional conflict.[26,27]

Strengths of the current review include the use of an extensive, systematic search strategy in five widely used databases from founding date through May 2018. We therefore believe the chance of having missed relevant studies is small. In addition, by limiting our inclusion of eligible studies to patients having received a diagnosis of lung cancer, our results provide important information on a relatively homogeneous patient population. Lastly, we adhered to the evidence-based PRISMA guidelines, thereby improving our study's reporting structure.[28]

Several limitations of this review deserve consideration. A number of studies in this review were powered to detect effects for a larger sample with different types of cancer being included. This might have resulted in insufficient power to detect effects in the subsample of lung cancer patients. A meta-analysis would have increased statistical power but was not possible due to heterogeneity of interventions and outcomes. Clinical relevance, however, is not effected by sample size and was clearly defined for most questionnaires in our study.

Furthermore, we decided to focus on effects of SDM on distress and healthcare utilization. We specifically opted for these outcomes since patients with lung cancer are faced with a poor prognosis, are highly distressed, and face difficult treatment choices when approaching the end of life.[65,66] The observation that subsamples of patients with lung cancer experienced higher levels of distress further supports this notion. Evidently, other outcomes such as quality of life, patient knowledge or patients' decisional satisfaction are also of relevance in this setting. Such outcomes were not included in the current study but should be a target of future studies, especially when SDM is explicitly facilitated through the use of a decision aid.

More work in this context is clearly needed. Development of a MESH term specifically detailing on SDM would be useful in the future. We had to perform a relatively broad search, including 49 terms to fully cover the concept of shared decision making and to ensure that all eligible studies were identified. Further, randomized studies may not be the most optimal mode to study potential benefits of SDM. This could especially be true for patients with lung cancer since the disease course is unpredictable and patients are faced with a poor prognosis. Yet, despite the relatively small differences, we did find positive effects on emotional outcomes (e.g. anxiety and depression) and healthcare use. In light of the overuse of aggressive therapies near the end of life,[65,67,68] facilitating SDM in the context of lung cancer may lead to improved well-being and better alignment of care to patients' personal preferences. Future studies should attempt to establish such associations and explicitly focus on measuring the effects of a decision aid, possibly by measuring the achievement of personalized goals. Ultimately, such studies could further elucidate mechanisms on how to facilitate SDM and provide patient-centered care for patients with lung cancer.

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SUPPLEMENTS

Supplement A. PICO and Search Strategy

Participants/population
Adult patients with lung cancer

Intervention(s), exposure(s)

Inclusions:
- Implementation of shared decision making: intervention designed to help people make specific and deliberative choices among options (including the status quo, symptom relief, treatment etc.)
- Use by patients or caregiver
- Content is relevant with regards to treatment decisions

Comparator(s)/control

Inclusions:
- Patient group which received usual care

Exclusions:
- Studies describing a comparison of SDM tools without a usual care arm

Outcomes

1. Distress with symptoms of either:
    - Distress (as separate scale or validated domain within a scale)
    - Anxiety
    - Depression
    - Quantified by a validated screening instrument (for example the Hospital Anxiety and Depression Scale)
2. Healthcare utilization
    - Chemotherapy administration
    - Hospital and GP visits
    - Hospitalizations
    - Emergency department visits
    - Hospice services
    - Location of death
    - Documentation of resuscitation preferences

Search

1. Shared decision making
2. Lung cancer
3. Distress
4. Healthcare utilization

1 AND #2 AND (#3 OR #4)

Search strings (Medline via EBSCO)

1 Shared decision making

((MH "Decision Making+") OR (MH "Decision Support Techniques+") OR (MH "Decision Support Systems, Clinical") OR (MH "Patient Preference") OR (MH "Patient Care Planning+")
OR (MH "Needs Assessment") OR (MH "Patient Participation") OR (MH "Patient-Centered Care+") OR (MH "Advance Care Planning+")
OR
TI "Treatment decision*" OR TI "decision aid*" OR TI "decision tool*" OR TI "communication aid*" OR TI "decision making" OR TI "decision support" OR TI preference* OR TI "goal* of care" OR TI "patient care planning" OR TI "need* assessment*" OR TI "care need*" OR TI "patient* need*" OR TI "patient participation" OR TI "patient centered care" OR TI "patient centred care" OR TI "advanc* care planning" OR TI "early palliative care" OR TI "integrated care" OR TI "supportive care" OR TI "integrated palliative care"
OR
AB "Treatment decision*" OR AB "decision aid*" OR AB "decision tool*" OR AB "communication aid*" OR AB "decision making" OR AB "decision support" OR AB preference* OR AB "goal* of care" OR AB "patient care planning" OR AB "need* assessment*" OR AB "care need*" OR AB "patient* need*" OR AB "patient participation" OR AB "patient centered care" OR AB "patient centred care" OR AB "advanc* care planning" OR AB "early palliative care" OR AB "integrated care" OR AB "supportive care" OR AB "integrated palliative care")

2 Lung cancer

((MH "Lung Neoplasms+")
OR
TI "Lung Neoplasm*" OR TI "Lung Cancer" OR (TI Lung AND TI Cancer) OR TI SCLC OR TI NSCLC OR TI "Lung carcinoma"
OR
AB "Lung Neoplasm*" OR AB "Lung Cancer" OR (AB Lung AND AB Cancer) OR AB SCLC OR AB NSCLC OR AB "Lung carcinoma")

3 Distress

((MH "Stress, Psychological+") OR (MH "Mood Disorders+") OR (MH "Anxiety+") OR (MH "Anxiety Disorders+") OR (MH "Depression") OR (MH "Depressive Disorder+")
OR
TI Distress OR TI "Symptom burden" OR TI Mood* OR TI Anxiety OR TI Depressi* OR TI
LCSS OR TI "Lung cancer symptom score" OR TI "Lung cancer symptom scale" OR TI "Interest question" OR TI "One-question interview" OR TI BAI OR TI BCD OR TI BDI OR TI BEDS

OR TI BSI OR TI "Brief Symptom Inventory" OR TI CES D OR TI DI C OR TI DT/PL OR TI ESAS OR TI "Edmonton Symptom Assessment" OR TI GHQ OR TI " General Health
Questionnaire" OR TI HADS OR TI HQ OR TI "Hornheide Questionnaire" OR TI IES OR TI "Impact of Event Scale" OR TI "Impact of Event Score" OR TI MEQ OR TI PDI OR TI PHQ
OR TI "Patient Health Questionnaire" OR TI POMS OR TI PSSCAN OR TI "Psychosocial Screen* for Cancer" OR TI RSCL OR TI "Rotterdam Symptom Checklist" OR TI ZSDS OR TI
GDS OR TI HRSD OR TI SAS OR TI SDS OR TI STAI OR TI SDS
OR
AB Distress OR AB "Symptom burden" OR AB Mood* OR AB Anxiety OR AB Depressi* OR AB LCSS OR AB "Lung cancer symptom score" OR AB "Lung cancer symptom scale" OR AB "Interest question" OR AB "One-question interview" OR AB BAI OR AB BCD OR AB BDI OR AB BEDS OR AB BSI OR AB "Brief Symptom Inventory" OR AB CES D OR AB DI C OR AB DT/PL OR AB ESAS OR AB "Edmonton Symptom Assessment" OR AB GHQ OR AB "General Health Questionnaire" OR AB HADS OR AB HQ OR AB "Hornheide Questionnaire" OR AB IES OR AB "Impact of Event Scale" OR AB "Impact of Event Score" OR AB MEQ OR AB PDI OR AB PHQ OR AB "Patient Health Questionnaire" OR AB POMS OR AB PSSCAN OR AB "Psychosocial Screen* for Cancer" OR AB RSCL OR AB "Rotterdam Symptom Checklist" OR AB ZSDS OR AB GDS OR AB HRSD OR AB SAS OR AB SDS OR AB STAI OR AB SDS)

4 Health care utilization

((MH "Delivery of Health Care+/UT") OR (MH "Hospitalization+") OR (MH "Hospice Care/UT") OR (MH "Emergency Medical Services+/UT") OR (MH "After-Hours Care+/UT") OR (MH "Health Services Administration+/UT") OR (MH "Intensive Care Units+/UT") OR (MH "Terminal Care+") OR (MH "Palliative Care") OR
TI "Healthcare utilization" OR TI "Healthcare utilization" OR TI "Resource* use" OR TI "Chemotherapy administration*" OR TI Hospitalization* OR TI Hospitalisation* OR TI "Hospital visit*" OR TI "Hospital day*" OR TI "Location of Death" OR TI "Death location" OR TI
"Emergency Department Visit*" OR TI "ED visit*" OR TI "General Practitioner visit*" OR TI "GP visit*" OR TI "Intensive Care Unit Day*" OR TI "ICU Day*" OR TI "Terminal care" OR TI "Palliative Care" OR TI "End of life care" OR TI "Care at the end of life" OR TI "Care at end of life"
OR
AB "Healthcare utilization" OR AB "Healthcare utilization" OR AB "Resource* use" OR AB "Chemotherapy administration*" OR AB Hospitalization* OR AB Hospitalisation* OR AB "Hospital visit*" OR AB "Hospital day*" OR AB "Location of Death" OR AB "Death location" OR AB "Emergency Department Visit*" OR AB "ED visit*" OR AB "General Practitioner visit*" OR AB "GP visit*" OR AB "Intensive Care Unit Day*" OR AB "ICU Day*" OR AB "Terminal care" OR AB "Palliative Care" OR AB "End of life care" OR AB "Care at the end of life" OR AB "Care at end of life")

Supplement B. Other measures of healthcare utilization

Source	ICU admissions	Location of death	Hospice	Composite score for aggressive end of life care	Other measures
Bakitas et al. (2014)[a]	Number of days in ICU between randomization and reference date: 0.0 days vs 0.5 days, p=0.16	-	-	-	-
Basch et al. (2016)[a]	-	-	-	-	-
Geerse et al. (2016)	-	Location of death: home 73% vs 71%; hospital 23% vs 21%, nursing home 2% vs 7%, hospice 2% vs 1%, p=0.59	-	Aggressive end of life care in last 14 days of life[b]: 46% vs 37%, p=0.25 Aggressive end of life care in last 30 days of life[b]: 63% vs 52%, p=0.19	-
King et al. (2016)	-	-	Hospice enrollment: 84% vs 74%, adjusted OR 1.86, p=0.113 Median hospice length of stay: 24 days vs 38.5 days, adjusted HR 0.70, p=0.041	-	
Nieder et al (2016)[f]	-	Hospital death: 33% vs. 47% vs. 50%, 0.28	-	-	Documented resuscitation preference :100% vs. 87% vs 76%, p=0.007 Documented earlier than in the last 3 months of life: 61% vs 12% vs 18%, p=0.0001
Reville et al. (2010)	Receiving ICU-care: 23.3% - - vs 25.4%[e]			Discharged to hospice: 6% vs 41%[e] Discharged to skilled nursing facility or rehabilitation home 13% vs 8%[e] Discharged to home 72% vs 17%[e]	-

Source	ICU admissions	Location of death	Hospice	Composite score for aggressive end of life care	Other measures
Temel et al. (2010) and Greer et al. (2012)	-	Location of death: home 54.5% vs 65.6%, p=0.28; inpatient hospice 19.7% vs 14.8%, p=0.49; hospital or nursing home or rehabilitation facility 25.8% vs 19.7%, p=0.53	Admission to hospice between randomization and death[c]: 65.7% vs 71.0%, p=0.57 Admission to hospice ≤ 3 days prior to death: 14.7% vs 3%[e] Admission to hospice > 7 days before death: 33.3% vs 60.0%, p=0.004 Median length of stay in hospice: 9.5 days vs 24.0 days, p=0.02	Aggressive end-of-life-care[d]: 54% vs 33%, p=0.05	-
Yount et al. (2014)	-	-	-		Mean number of unscheduled clinic visits during 12 weeks: 0.25 vs 0.41, p=0.13 Mean number of phone calls to physicians during 12 weeks: 0.81 vs 0.85, p=0.32 Mean number of phone calls to nurses during 12 weeks: 1.14 vs 1.79, p=0.02

Data on usual care group versus intervention group are displayed. Abbreviations: OR: Odds Ratio, provided with 97% confidence interval. HR: Hazard Ratio: provided with 95% confidence interval

[a] The complete study included a larger sample of patients with different types of cancer. Data of the subsample of patients with lung cancer is displayed in this table.

[b] Patients receiving chemotherapy, being hospitalized, or visiting the ED within either the last 14 or 30 days before death were documented as having received aggressive end-of-life care

[c] Median duration of follow up among participants who died 5.7 months.

[d] Patients receiving chemotherapy within 14 days before death, no hospice care, or admission to hospice 3 days or less before death were documented as having received aggressive end-of-life care

[e] No p-value provided

[f] Early palliative care vs. late palliative care vs. no palliative care

III

Chapter 3

Structural distress screening and supportive care for patients with lung cancer on systemic therapy: A randomised controlled trial

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ABSTRACT

Introduction: Gaining regular insight into the nature and severity of distress by a psychosocial nurse coupled with referral to psychosocial and/or paramedical healthcare provider(s) is an experimental supportive care approach. We sought to examine the effects of this approach on quality of life (QoL), patient's mood and satisfaction, end-of-life care, and survival in patients with lung cancer.

Methods: Patients with newly diagnosed or recurrent lung cancer starting systemic therapy were randomly assigned to receive usual care or the experimental approach. Patients were followed up at 1, 7, 13, and 25 weeks after randomization with the EORTC-QLQ-C30, the European Quality of Life-5D, the Hospital Anxiety and Depression Scale, and the Patient Satisfaction Questionnaire-III. Primary outcome was the mean change in the EORTC-QLQ-C30 global QoL-score between 1 and 25 weeks.

Results: A total of 223 patients were randomized of whom 111 (50%) completed all four assessments (44% in the usual care group vs. 55% in the experimental group). No significant difference was found in the mean change global QoL-score (-2.4, 95% CI - 12.1–7.2; $P = 0.61$), nor in the other patient-reported outcomes. Fewer patients in the experimental group received chemotherapy shortly before the end-of-life and median survival was comparable (10.3 vs. 10.1 months, $P = 0.62$). Of the 112 dropouts, 33 died and 79 discontinued participation for other reasons.

Conclusions: Our supportive care approach did not improve QoL nor other patient-reported outcomes in patients with lung cancer. However, it reduced the use of chemotherapy shortly before the end of life. Possibly, QoL-improvements may have been obscured by (late) side-effects of systemic therapy.

INTRODUCTION

The integration of supportive care is increasingly recognized as important in comprehensive cancer treatment to improve patients' quality of life (QoL) and well-being.[1–4] However, barriers still exist when integrating supportive care into usual care and there is no consensus on the optimal timing and the most appropriate mode.[5] Currently, no uniform definition of best supportive care practice exists and it is often poorly defined. A recent review does provide a set of consensus-based domains offering a framework for supportive care practices. Four key domains are defined in this framework: multidisciplinary care, supportive care documentation, symptom assessment, and symptom management.[6] Nonetheless, current supportive care practices within oncology still vary with regards to implementation, scope, and intensity.

Approximately 60% of patients with lung cancer experience distress during or after treatment.[7,8] Distress itself is defined as 'a multifactorial unpleasant emotional experience of a psychological, social and/or spiritual nature that may interfere with the ability to cope effectively.[9] We hypothesized that providing additional supportive care via an approach aimed at alleviating distress would improve the QoL of patients with lung cancer.

The basis for such an approach is postulated in the guideline on "Screening of Distress and Referral Need".[10] This approach consists of three steps: 1) gaining regular insight into the level and nature of patients' distress by a self-administered distress screening tool 2) discussion of its responses with a dedicated nurse and 3) referral to psychosocial and/or paramedical health caregivers if needed or wished by the patient. It is aimed at reducing distress and is thereby thought to improve the QoL of patients with cancer. Timely detection of potential sources of distress (e.g. pain or feelings of sadness) and provision of targeted interventions are key to this process. We used the guideline on "Screening of Distress and Referral Need" as the basis for our intervention and sought to compare this experimental approach to usual care alone by examining the effects on QoL, mood, patient satisfaction, and the impact on end-of-life care in patients with lung cancer on systemic therapy.

METHODS

Patients and procedure

All patients consecutively diagnosed in the University Medical Center Groningen with newly diagnosed (stage Ib to IV) or recurrent lung cancer were eligible when starting either chemotherapy, adjuvant chemotherapy, chemo-radiotherapy, or treatment with biologicals, and having an Eastern Cooperative Oncology Group (ECOG) performance score between 0 and 2. Patients were excluded if there was actual psychiatric co-morbidity, as diagnosed by a psychiatrist, or when already receiving care from a palliative team.

Eligible patients were informed about the study by their treating physician and invited to participate within a week after start of therapy. All patients were asked to complete questionnaires at home at four time points coinciding with scheduled outpatient visits: 1, 7, 13, and 25 weeks after randomization (T1 at baseline, through T4). Since improvements in QoL are not likely during the administration of systemic therapy (generally 12 weeks), we chose a relatively late outcome at 25 weeks to observe effects on QoL after cessation of systemic therapy.

Randomization, questionnaire distribution, and data management were performed by the Netherlands Comprehensive Cancer Organisation (IKNL). The hospital medical ethics committee approved the protocol and all patients provided written informed consent.

Randomization

Patients were randomized to receive either usual care or the experimental approach in a 1:1 ratio. Performance score and disease stage were used as stratification factor.[11] The randomization schedule was generated by a validated system (PMX CTM, release 3.3.0 HP2, Propack Data) with the use of a pseudo–random number generator and a supplied seed number.

Usual care

Usual care for patients consisted of medical and (psycho-)social care offered by the treating physician every 3 weeks. Specific psychosocial care was not routinely integrated in usual care and referral to appropriate healthcare professionals was performed by the treating physician only based on clinical judgement. Additional care was scheduled ad hoc and there was no structural screening of distress. Oncology or research nurses were not involved unless requested by the treating physician.

Experimental approach

Patients in the experimental group completed the Distress Thermometer and Problem List (DT/PL) before their scheduled outpatient clinic appointment at baseline through T4. After completion of the DT/PL, patients met face-to-face with a psychosocial nurse to discuss their response pattern. Patients were offered referral to an appropriate and licensed healthcare professional if the Distress Thermometer score was >4 or if a patient only answered the referral wish question with 'yes' (see Supplemental Figures A and B). Referral was based on the experienced problems in specific life domains (e.g. a physiotherapist for physical problems). All patients were offered a minimum of four meetings with a psychosocial nurse (baseline through T4) and allowed to schedule additional meetings when requested.

The DT/PL, a validated distress screening instrument,[12,13] consists of the Distress Thermometer, Problem List, and the referral wish question (yes, maybe, no). The Distress Thermometer is

a single-item, self-report measure of distress experienced over the past week ranging from 0 (no distress) to 10 (extreme distress). A score of 4 has been recommended as an optimal cut-off for referral.[12] The Distress Thermometer score was not used as an outcome measure. The Problem List consists of 47 items covering five life domains: practical (7 items), social (3 items), emotional (10 items), spiritual (2 items), and physical (25 items).

Outcome measures and data collection

All patients completed the EORTC-QLQ-C30 and the lung-cancer module (EORTC-LC13). The 30-item EORTC-QLQ-C30 assesses QoL in six dimensions: global QoL, physical functioning, role performance, and emotional, cognitive, and social functioning.[14] The 13-item EORTC-LC13 evaluates symptoms specific for lung cancer.[15]

To further assess QoL, mood, and patient satisfaction, patients completed the European Quality of Life 5-Dimensions questionnaire (EQ-5D), the Hospital Anxiety and Depression Scale (HADS), and the Patient Satisfaction Questionnaire-III (PSQ-III) at baseline through T4.[16–18] The 43-item PSQ-III assesses patient satisfaction with received care.[18] The questionnaire focuses on five aspects of satisfaction with care: total satisfaction, overall satisfaction, accessibility of care, interpersonal manner, and technical quality. Scores range from 0-100, with higher scores reflecting higher satisfaction.

Data on sociodemographic characteristics and the Charlson comorbidity score[19] were collected for all patients at study entry. Prognostic variables, disease progression, and date of death were derived from the digital patient information system.

Post-hoc analysis

As a post-hoc analysis to assess end-of-life care, data on chemotherapy administration, hospital admissions, emergency department (ED) visits, and location of death were obtained from all patients who had died at the start of analyses.[20]

Statistical analysis

Statistical analyses were performed using SPSS software version 20. Power calculations were based on the primary outcome: the mean change in the global QoL-score from the EORTC-QLQ-C30 between baseline and T4. Assuming a difference between groups of at least 10 points on the global QoL-score (the minimal clinically significant change is 8 - 10 points[21]) and a standard deviation of 24.3, 188 patients were to be included with an alpha = 0.05, and a 1-beta = 0.80. Anticipating a dropout rate of 30%, the aim was to include a total of 250 patients.

Independent Student's t-tests were used to investigate the difference in the primary outcome, i.e. change from baseline to T4 (25 weeks) between the two groups. In addition, we conducted a linear mixed models analysis to examine change over time, differences between groups, and interaction effects. Participants who completed the full study period (so called completers) were compared to those who dropped out (so called dropouts) on all baseline variables. Overall survival was calculated from date of randomisation to date of death and analysed by the log-rank test and Kaplan-Meier method. Secondary outcomes were not corrected for multiple comparisons since they were exploratory only. Statistical tests were performed with two-sided alternatives and considered significant if $P \leq 0.05$.

RESULTS

Patients

Between January 2010 and June 2013, 591 patients were screened for eligibility. Of the 337 eligible patients, 223 (66%) patients consented to participate and were randomized (Figure 1). Twenty-eight patients discontinued participation and did not complete baseline assessment. A total of 195 completed baseline questionnaires and 111 patients (50%) completed all four assessments: 50 patients (44%) in the usual care group and 61 (55%) in the experimental group. Of the remaining 112 patients (50%) who did not complete the full study period, 33 (15%) died during the study period (13 patients in the usual care group (12%) and 20 patients in the experimental group(18%); $P = 0.23$). The other 79 patients (35%) discontinued participation (50 patients in the usual care group (44%) and 29 patients in the experimental group (26%); $P = 0.05$). The number of meetings patients assigned to the experimental group had with the psychosocial nurse is outlined in Supplemental Table A.

Dropouts versus completers

Dropouts ($N = 112$) had a worse performance score at baseline than the completers ($N = 111$) in both groups ($P < 0.01$) and a higher mean Charlson co-morbidity score ($P < 0.05$ in both groups). Additionally, dropouts had lower mean scores at baseline on the EORTC-QLQ-C30 global QOL, physical functioning, and role performances (all $P < 0.02$); a lower mean EQ-5D total and self-rated health score (all $P < 0.02$); and worse depression scores (higher mean depression scores in both groups, $P = 0.05$) than the completers. Moreover, more dropouts in the experimental group had stage IV disease ($P < 0.01$) and their Charlson age-adjusted mean score was higher ($P = 0.01$) compared to completers.

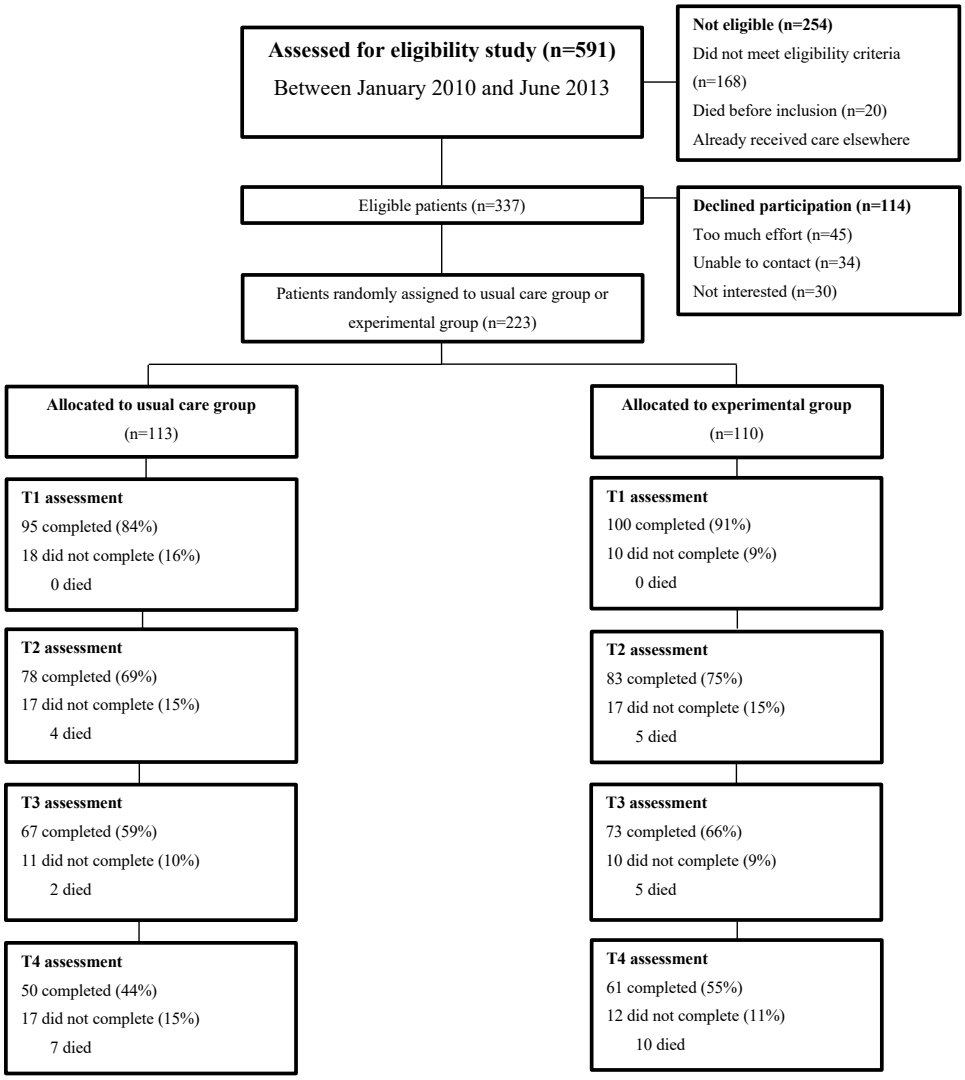

FIGURE 1. CONSORT Flow Diagram

Interim analysis

A substantially higher drop out than originally anticipated (30%) was encountered at 25 weeks thereby compromising our original power calculations. Therefore, our ethics committee agreed on the conduction of an interim analysis. This analysis was subsequently performed by an independent statistician with preset decision rules on whether to continue recruitment of patients to compensate for larger drop-out rates or to stop study inclusion.

Data from 188 patients between baseline and T3 were analyzed. The interim analysis revealed no significant effect nor a trend towards significance in our primary outcome. Consequently, study inclusion was stopped before the originally calculated number of 250 patients was reached.

Baseline characteristics

The two groups were similar except that more patients smoked and more received chemo-radiation in the experimental group (Table 1 and Supplemental Table B).

Per-protocol analysis

No significant difference between the two groups in the primary outcome nor the mean change in the global QoL score of the EORTC-QLQ-C30 from baseline to T4 was found (-2.4, 95% CI -12.1 – 7.2; P = 0.61; Table 2). The mean change between baseline and T4 in EORTC-QLQ-C30 subscales, in EQ-5D total score, and in HADS scores showed no significant differences between both groups (Table 2). Also, mean change scores on the specific lung cancer module of the EORTC-QLQ-C30 and PSQ-III did not reveal any significant differences. Of note, the mean scores on all PSQ-III subscales were high in at all time points in both study groups (> 75).

Intention-to-treat analysis

A linear mixed models analysis, conducted to better approximate an intention-to-treat analysis, showed no significant differences in the global QoL-score between the two groups (data not shown).

Progression of disease, end-of-life care, and survival

Follow up of all patients was until death or at least 25 weeks (T4). Disease progression was comparable between the groups (84% of patients in the usual care group vs. 83% of patients in the experimental group; P = 0.79). Of the 223 patients, 153 (69%) had died.

TABLE 1. Baseline Characteristics of 223 patients with lung cancer on systemic therapy randomized to usual care versus structural distress screening and psychosocial support (experimental group) at baseline

Variable	Usual care group (*N*=113)	Experimental group (*N*=110)
Age in years (mean±SD)	62.3 ± 9.7	60.6 ± 10.5
Female sex (N(%))	44 (39)	50 (46)
Marital status (N(%))[a]		
Married/cohabiting	80 (71)	75 (68)
Living apart together	1 (1)	4 (4)
Single	5 (4)	12 (11)
Divorced/separated	4 (4)	2 (2)
Widowed	7 (6)	8 (7)
Performance status at inclusion (N(%))		
0	52 (46)	46 (42)
1	52 (46)	56 (51)
2	9 (8)	8 (7)
Recurrent disease, yes (N(%))	35 (31)	29 (26)
Brain metastases at inclusion (N(%))	14 (12)	16 (15)
Disease stage (N(%))		
Stage 1 or 2	10 (9)	10 (9)
Stage 3	21 (19)	29 (26)
Stage 4	82 (72)	71 (65)
Smoking (N(%))[†]		
Yes	35 (31)	48 (44)
Quit	55 (49)	51 (46)
No	23 (20)	11 (10)
Charlson co-morbidity score (mean±SD)	6.0 ± 1.8	5.7 ± 2.1
Histology (N(%))		
Adenocarcinoma	71 (63)	64 (58)
Squamous cell carcinoma	17 (15)	19 (17)
Large cell n.o.s.	5 (5)	5 (5)
Small-cell carcinoma	14 (12)	20 (18)
Other	6 (5)	2 (2)
Type of mutation (N(%))		
EGFR	13 (12)	9 (8)
ALK	7 (6)	7 (7)
KRAS	24 (21)	11 (10)
BRAF	0 (0)	1 (1)
No mutation	28 (25)	31 (28)
Unknown	6 (5)	10 (9)
Not applicable	35 (31)	41 (37)

TABLE 1. Continued

Variable	Usual care group (*N*=113)	Experimental group (*N*=110)
Mutation tested (N(%))		
Yes	72 (64)	59 (54)
No	6 (5)	10 (9)
Not applicable	35 (31)	41 (37)
Treatment at inclusion (N(%))[a]		
Chemotherapy	79 (70)	60 (55)
Chemo-radiotherapy	12 (11)	29 (26)
Biological	22 (19)	21 (19)
EORTC-QLQ-C30[b] score (mean±SD)		
Global quality of life (*N*=194)	57.7 ± 24.0	59.2 ± 20.8
Physical functioning (*N*=194)	64.2 ± 25.9	67.5 ± 24.0
Role performance (*N*=193)	50.7 ± 32.3	50.8 ± 32.0
Emotional functioning (*N*=194)	73.0 ± 21.6	72.4 ± 22.6
Cognitive functioning (*N*=194)	77.2 ± 22.6	80.0 ± 21.0
Social functioning (*N*=193)	69.9 ± 24.8	75.6 ± 21.9
EQ-5D[c] score (mean±SD)		
Total score (*N*=191)	0.7 ± 0.3	0.7 ± 0.3
Health scale score (*N*=186)	62.6 ± 17.1	62.6 ± 18.7
HADS[d] score (mean±SD)		
Total score (*N*=189)	13.5 ± 9.5	12.6 ± 7.1
Anxiety subscale (*N*=190)	6.9 ± 4.8	6.4 ± 4.1
Depression subscale (*N*=192)	6.7 ± 5.3	6.2 ± 3.9
PSQ-III score (mean±SD)		
Total satisfaction (*N*=183)	84.4 ± 12.9	84.1 ± 11.4
Overall satisfaction (*N*=182)	81.3 ± 19.0	82.3 ± 16.9
Accessibility (*N*=183)	80.5 ± 14.1	81.1 ± 12.1
Interpersonal manner (*N*=187)	87.4 ± 15.4	88.3 ± 12.0
Technical quality (*N*=183)	83.5 ± 14.7	82.2 ± 15.4

a Analysis was performed over two groups: married/co-habiting versus people living alone (categories: living apart together, single, divorced/separated, or widowed). In addition, numbers of respondents varies and percentages do not add up to 100 percent since not all patients completed all questions † Significant differences between groups noted.

b The 30-item EORTC-QLQ-C30 assesses QOL. Scores can range from 0-100 with higher scores reflecting better functioning.

c The five-item European Quality of Life 5-Dimensions (EQ-5D) assesses QOL using a three point response scale with higher scores indicating better functioning. Conjointly, a visual analogue scale assesses self-rated health (range 0-100).

d The Hospital Anxiety and Depression Scale (HADS) assesses anxiety and depression levels over the last week in two subscales each consisting of seven items. Scores vary from 0 to 21 with higher scores indicating greater anxiety or depression.

TABLE 2. Comparison of mean change in EORTC-QLQ-C30, EQ-5D, and HADS scores between baseline and T4

Variable	Usual care group Mean change from baseline score[a] (*N*=50)	Experimental group Mean change from baseline score[a] (*N*=61)	Difference between groups [95% CI]	*P*-value
EORTC-QLQ-C30 score (mean±SE)				
Global quality of life (*N*=109)	5.8 ± 3.6	3.3 ± 3.3	-2.4 [-12.1 – 7.2]	0.61
Physical functioning (*N*=110)	-1.2 ± 3.0	-3.5 ± 2.9	-2.3 [-10.6 – 6.0]	0.58
Role performance (*N*=109)	0.7 ± 4.8	6.9 ± 4.8	6.3 [-7.4 – 20.0]	0.37
Emotional functioning (*N*=109)	1.7 ± 3.5	6.4 ± 2.6	4.7 [-3.8 – 13.3]	0.28
Cognitive functioning (*N*=109)	2.0 ± 3.3	2.5 ± 2.6	0.5 [-7.7 – 8.6]	0.91
Social functioning (*N*=109)	4.4 ± 3.4	6.1 ± 3.7	1.7 [-8.3 – 11.7]	0.74
EQ-5D score (mean±SE)				
Total score (*N*=106)	-0.004 ± 0.03	-0.01 ± 0.04	-0.009 [-0.1 – 0.1]	0.85
Health scale score (*N*=102)	-1.2 ± 2.7	-0.78 ± 3.1	0.45 [-7.9– 8.8]	0.92
HADS score (mean±SE)				
Total score (*N*=106)	-2.4 ± 1.3	-2.1 ± 1.0	0.3 [-2.8 – 3.5]	0.85
Anxiety subscale (*N*=107)	-1.3 ± 0.7	-1.3 ± 0.5	0.02 [-1.6 – 1.6]	0.98
Depression subscale (*N*=108)	-0.9 ± 0.7	-0.6 ± 0.6	0.3 [-1.6 – 2.1]	0.77
PSQ-III score (mean±SE)				
Total satisfaction (*N*=102)	3.4 ± 1.7	-0.3 ± 1.7	-3.7 [-8.5 – 1.1]	0.13
Overall satisfaction (*N*=103)	4.6 ± 2.6	-1.4 ± 3.1	-6.0 [-14.1 – 2.1]	0.15
Accessibility (*N*=101)	5.4 ± 2.0	1.2 ± 1.9	-4.2 [9.7 – 1.2]	0.13
Interpersonal manner (*N*=104)	3.1 ± 2.1	-1.2 ± 2.0	-4.3 [-10.1 – 1.6]	0.15
Technical quality (*N*=102)	1.2 ± 2.0	-0.9 ± 2.3	-2.2 [-8.3 – 4.0]	0.49

Standard errors (± SE) are displayed.

a Mean change scores were calculated as the mean T4 score minus the mean baseline score. A positive mean change score thus signifies a higher score on that specific subscale

Fewer patients in the experimental group received chemotherapy in their last month of life (P = 0.03). Other indicators of aggressive end-of-life care were not significantly different but showed numerical trends in the same direction favoring the experimental group (Table 3). Median survival time was comparable at 10.1 months (95% CI, 7.6 - 12.6) in the usual care group vs. 10.3 months (95% CI, 6.5 - 14.1) in the experimental group; P = 0.62 (Figure 2).

TABLE 3. Differences between study groups in end-of-life care indicators of deceased study participants

Variable	Usual care group *N*=80 (%)	Experimental group *N*=73 (%)	*P*-value
Chemotherapy administration			
Chemotherapy within 14 days before death	9 (11)	3 (4)	0.10
Chemotherapy within 30 days before death	21 (26)	9 (12)	0.03
Hospitalizations			
Any admission(s) from randomization to death	61 (76)	53 (73)	0.61
Any admission(s) within 14 days before death	34 (43)	24 (33)	0.22
Any admission(s) within 30 days before death	45 (56)	34 (47)	0.23
Emergency Department (ED) Visits			
Any ED visit(s) from randomization to death	55 (69)	42 (58)	0.15
Any ED visit(s) within 14 days before death	20 (25)	13 (18)	0.28
Any ED visit(s) within 30 days before death	30 (38)	18 (25)	0.09
Location of death			
Home	58 (73)	52 (71)	
Hospital	18 (23)	15 (21)	
Nursing home	2 (2)	5 (7)	0.59
Hospice	2 (2)	1 (1)	
Aggressive end-of-life care[a]			
Received within last 14 days of death, yes	37 (46)	27 (37)	0.25
Received within last 30 days of death, yes	50 (63)	38 (52)	0.19

a Patients receiving chemotherapy, being hospitalized, or visiting the ED within either the last 14 or 30 days before death were documented as having received aggressive end-of-life care

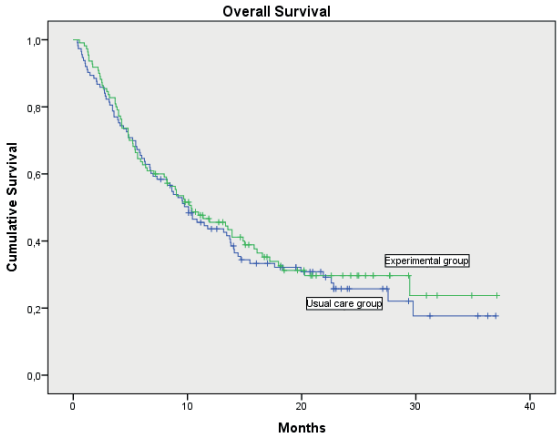

FIGURE 2. Kaplan Meier overall survival curve according to study group. Survival was calculated from the date of randomization until the date of death. Date of death was recorded up to the start of the analysis at 01-01-2014.

DISCUSSION

In our study, we investigated the effects of a supportive care approach by structural implementation of distress screening, referral, and additional psychosocial support for patients with lung cancer on systemic therapy. This approach did not offer benefits in terms of QoL or other patient-reported outcomes when compared to usual care alone. As a possible readout of less aggressive end-of-life care, significantly fewer patients in the experimental group received chemotherapy in their last month of life.

Several aspects need to be considered as to why this supportive care approach did not offer benefits to QoL in our study. First, patient satisfaction with usual oncology care throughout the study period was similar and high throughout the entire study period. This ceiling effect may have masked additional effects of our supportive care intervention and may suggest that usual care may already have been optimal from a patients' perspective and may suggest that usual care alone may already have been optimal from a patients´ perspective. Second, based on the results of our interim analysis, study inclusion was stopped early at 223 patients since not even a trend towards a significant effect in our primary outcome was found.

Third, dropouts had significantly lower scores on disease-related parameters and outcome measures suggesting that they were relatively sicker at baseline compared to the completers of the study. Yet, most of these differences were detected in dropouts of both study groups and thus less likely to significantly affect our study outcome. In addition, no significant baseline QoL difference was found among the completers in both groups thus eliminating a possible selection bias. Lastly, our QoL measurement outcome may not have been sensitive or specific enough to detect relevant effects of our intervention. Other outcome measures, such as the Edmonton Symptom Assessment Scale[22] or a generic well-being measure, may have been more appropriate in this setting.

We observed that patients in the experimental group received less chemotherapy in their last month of life. Moreover, numerical trends were found in other indicators of aggressive end-of-life treatment (hospital admissions and ED visits[20]) favoring the experimental group. The timing and stopping of treatment at the end of life is a challenge both for physicians and patients. As such, avoiding futile care and enabling timely and effective palliative care is nowadays also regarded as a physicians' duty.[23] Similar effects of comparable interventions on end-of-life care indicators and economic outcomes have been shown by previous studies in, amongst others, patients with lung cancer.[24–26] However, further studies are needed to understand the mechanisms behind these findings. In addition, no data on the number of referrals was available in the current study. Future studies should include these data to compare uptake of services.

Earlier studies, although performed in mixed populations of patients with advanced cancer detailing on interventions not specifically designed to reduce distress, have yielded conflicting results. Two studies with a comparable study design in patients with advanced cancer showed no significant benefits of different supportive care interventions on QoL.[27,28] Moreover, a recent study concludes that completion of a QoL-questionnaire coupled with discussion of these responses with the treating physician is not likely to improve QoL. Yet, it does facilitate communication and targeted interventions aimed at tackling these issues.[29]

Additionally, a review study on distress screening concludes that the effects of providing supportive care to those found through screening and coupled interventions are ambiguous. It may be likely that screening coupled with a mandatory intervention, instead of an intervention based on the distress score and referral wish, is more effective.[30]

Yet, several similar studies did establish benefits of similar interventions on QoL, mood, symptom understanding, or survival in mixed cancer populations.[24,26,31,32] It has been suggested that the survival benefit found in two of these studies may be due to less aggressive treatment choices or earlier use of hospice services.[24,31] Still, this effect is most likely multifactorial and it remains unclear which element(s) of an intervention may account for the survival benefit found.[33] Additionally, notable methodological variations in the implementation of the interventions, heterogeneous study populations, and other study imbalances makes comparison difficult.[34] Also, patients with lung cancer reportedly experience higher levels of distress.[35,36] It may therefore be likely that that distinct interventions are required to offer clinically relevant benefits to patients with lung cancer.

Strengths of the current study were the large number of randomized patients (N=223). The study group was rather homogenous in that patients were only included if they started a form of systemic therapy. Yet, (late) side-effects of systemic therapy may have obscured possible improvements in QoL of our intervention. In addition, all patients with lung cancer visiting the outpatient clinic of our hospital were assessed for eligibility thereby reducing a selection bias. Also, overall similarity between groups at the start of the study was adequately balanced. Lastly, we employed the DT/PL which is a validated and widely used distress screening tool for patients with cancer.[12,37]

On the whole, our supportive care approach did not appear to offer QoL benefits to patients with lung cancer starting systemic therapy although benefits were found in previous studies. However, our study does show a possible effect on several indicators of aggressive end-of-life care. Additional qualitative investigations in similar settings would be needed to elucidate which aspects of current clinical practice may explain these findings.

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SUPPLEMENTS

SUPPLEMENTAL TABLE A. Number of meetings with the psychosocial nurse of patients assigned to the experimental group

Total number of meetings	Patients assigned to experimental group (%) n=110
0	10 (9)*
1	6 (5)
2	16 (15)
3	18 (16)
4	50 (46)
5	6 (5)
6	2 (2)
7	2 (2)

a As detailed in the CONSORT Flow Diagram, these 10 patients dropped out before the first scheduled meeting with the psychosocial nurse and therefore did not have any meetings with the psychosocial nurse.

Supplemental Table B. Extended baseline characteristics of study participants

Table 1 supplementary	**Usual care group (N=113)**	**Experimental group (N=110)**
Pack years (median, interquartile range)[a]	25, 6-40	30, 16-50
Children living at home, yes (N(%))*	19 (17)	22 (20)
Educational level (N(%)[b]		
High	33 (29)	29 (26)
Medium	46 (41)	51 (46)
Low	16 (14)	19 (17)
Work status (N(%)[b]		
Employed	13 (12)	15 (14)
Other (household, retired, studying, looking for job)	55 (49)	41 (37)
Unable to work	26 (23)	40 (36)
Inclusion in a clinical trial (N(%)[b]	48 (43)	40 (36)
Line of treatment (N(%))		
1	78 (69)	81 (73)
2	18 (16)	14 (13)
3 or more	17 (15)	15 (14)
Previous malignancy, yes (N(%)[b]	17 (15)	21 (19)

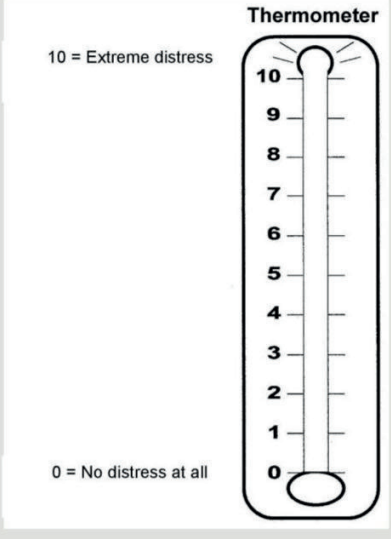
Data are mean (SD) or n (%).

a Significant differences between treatment arms noted.† Numbers of respondents vary slightly and percentages do not add up to 100 percent since not all patients completed all questions

Distress thermometer and problem list

Date of today: ..... - ..... - ..... (day-month-year)

First, please circle the number on the thermometer that best describes how much distress you have been experiencing in the past week (including today) physically, emotionally, socially, practically and religiously.



Source NCCN, USA

Problem list

Second, please indicate by checking yes or no if any of the following has been a problem for you in the past week (including today). Be sure to check YES or NO for each.

Yes	No	Practical problems
O	O	child care
O	O	housing
O	O	housekeeping
O	O	transportation
O	O	work/school/study
O	O	financial
O	O	insurance
		Family / social problems
O	O	dealing with partner
O	O	dealing with children
O	O	dealing with friends/family
		Emotional problems
O	O	keeping emotions under control
O	O	memory
O	O	self confidence
O	O	fears
O	O	depression
O	O	tension/nervousness
O	O	loneliness
O	O	concentration
O	O	feelings of guilt
O	O	loss of control
		Religious/spiritual concerns
O	O	meaning of life
O	O	trust in God / religion

Yes	No	Physical problems
O	O	appearance
O	O	changes in urination
O	O	constipation
O	O	diarrhoea
O	O	eating
O	O	feeling swollen
O	O	fever
O	O	mouth sores
O	O	nausea
O	O	nose dry/congested
O	O	pain
O	O	sexual
O	O	skin dry/itchy
O	O	sleep
O	O	shortness of breath/breathing
O	O	nausea
O	O	speech/talking
O	O	taste
O	O	weight change
O	O	tingling in hands/feet
O	O	bathing/ dressing
O	O	daily activities
O	O	fatigue
O	O	out of shape/condition
O	O	muscle strength

Other problems?

_____

Would you like to talk with someone about your problems?

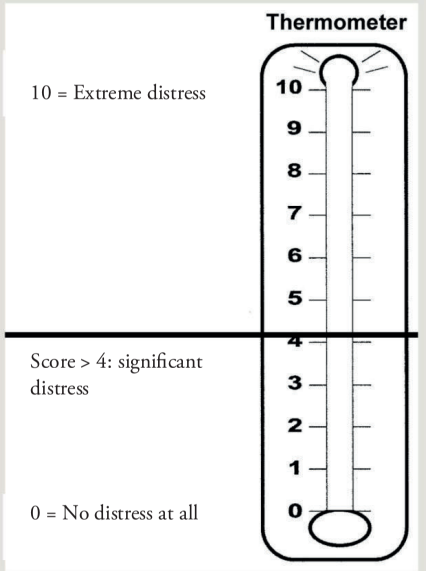
O yes O maybe O no

If yes, with whom?

O nurse O pastoral worker
O dietician O psychologist
O physiotherapist O patient association
O social worker O another, namely.....

SUPPLEMENTAL FIGURE A. The Distress Thermometer and Problem List (DT/PL)

Step 1: Completion of the Dutch Distress Thermometer, Problem List and referral wish question (DT/PL)



Step 2: Discussion of DT/PL responses

Responses on the DT/PL will be discussed with the nurse. The nurse checks for understanding and asks if any other problems currently exist that are not in the PL. The patient may be asked to rate the severity of each problem ticked or each domain by giving a score between 0–10.

Referral is offered when the Distress Thermometer score is >4 or a patient answers the referral wish question with 'yes'.

The need for referral will be discussed with the patient and the nurse. If the patient agrees to be referred, the nurse explains how the referral process works and refers the patient to one or more healthcare professionals.

Lastly, an appointment for the next meeting is made. The total appointment should last no longer than 1 hour.

Step 3: Referral

Referral to a healthcare professional varies according to the problems experienced. Broadly for:

Practical problems
- Social worker

Social problems
- Social worker
- Psychologist

Emotional problems
- Social worker
- Psychologist
- Psychiatrist (for psychiatric disorders, such as an anxiety disorder or depression, requiring adequate (medical) treatment by a psychiatrist)

Spiritual problems
- Pastoral worker

Physical problems
- Nurse specialist
- Physiotherapist
- Dietician
- Speech therapist
- Liasion nurse (When adequate and specialist care at home is required)
- Occupational therapist
- Palliative care nurse (For palliative care nursing questions)

Possible external referrals:
- Hospice
- Patient association
- Lung rehabilitation center

SUPPLEMENTAL FIGURE B. Using the DT/PL

IV

Chapter 4

The Distress Thermometer as a prognostic tool for one-year survival among patients with lung cancer

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ABSTRACT

Introduction: The use of patient-reported outcome measures is increasingly advocated to support high-quality cancer care. We therefore investigated the added value of the Distress Thermometer (DT) when combined with known predictors to assess one-year survival in patients with lung cancer.

Methods: All patients had newly diagnosed or recurrent lung cancer, started systemic treatment, and participated in the intervention arm of a previously published randomised controlled trial. A Cox proportional hazards model was fitted based on five selected known predictors for survival. The DT-score was added to this model and contrasted to models including the EORTC-QLQ-C30 global QoL score (quality of life) or the HADS total score (symptoms of anxiety and depression). Model performance was evaluated through improvement in the -2 log likelihood, Harrell's C-statistic, and a risk classification.

Results: In total, 110 patients were included in the analysis of whom 97 patients accurately completed the DT. Patients with a DT score 5 (N=51) had a lower QoL, more symptoms of anxiety and depression, and a shorter median survival time (7.6 months vs 10.0 months; P=0.02) than patients with a DT score <5 (N=46). Addition of the DT resulted in a significant improvement in the accuracy of the model to predict one-year survival (P<0.001) and the discriminatory value (C-statistic) marginally improved from 0.69 to 0.71. The proportion of patients correctly classified as high risk (85% risk of dying within one year) increased from 8% to 28%. Similar model performance was observed when combining the selected predictors with QoL and symptoms of anxiety or depression.

Conclusions: Use of the DT allows clinicians to better identify patients with lung cancer at risk for poor outcomes, further explore sources of distress, and personalize care accordingly.

INTRODUCTION

Lung cancer is the second most common and deadliest cancer worldwide. It constitutes approximately 14 percent of all cancer diagnoses and 27 percent of all cancer deaths.[1] Most patients are diagnosed with either locally advanced or metastatic disease and are often faced with treatment-related toxicities and side-effects.[2] These factors contribute to a poor prognosis, high levels of distress, and a lower quality of life (QoL) among patients and their caregivers.[3,4]

Despite this poor prognosis and limited survival, many patients with lung cancer receive aggressive treatments (e.g. chemotherapy) near the end of their life. Discussions focused on discussing the rationale for such treatments or patient's goals and values either happen late in the disease course or are of insufficient quality.[5] Moreover, it may be difficult to accurately determine a patient's prognosis due to the unpredictability of the disease course. Indeed, previous work shows that current prognostic predictions by clinicians are frequently inadequate and largely based on disease-related characteristics.[6,7] Recent studies have thus suggested that addition of patient-reported outcome measures (PROMs) to such predictions can be useful to better approximate a patient's prognosis.[8–11] Use and subsequent discussion of such measures also leads to better symptom control, increased use of supportive care facilities or measures, and enhanced patient satisfaction.[12]

A PROM has been defined as "a measurement of any aspect of a patient's health status that comes directly from the patient".[13] International and consensus-based guidelines advocate the routine use of PROMs as an integral component of high-quality cancer care.[9,11,14–16] To date however, these measures are only sparsely incorporated in clinical care for patients with (lung) cancer.[17,18] One example of a possibly useful rapid assessment tool is the Distress Thermometer (DT). The DT is a single-item, visual analogue scale that can be immediately interpreted to rule out elevated levels of distress in patients with cancer.[19,20] The prognostic value of this tool for survival has not been confirmed among patients with lung cancer.[21] To this end, we sought to investigate the prognostic value of the DT when combined with sociodemographic and clinical predictors to assess one-year survival in patients with lung cancer. We also compared this model to models that included scores on quality of life or symptoms of anxiety and depression.

METHODS

Design and setting

This study represents a secondary analysis of data obtained from a randomised controlled trial (RCT) evaluating the effects of screening for distress using the DT, the associated Problem List (PL) and additional supportive care measures to those in need of such care. This study detailed on the effects of this intervention on QoL, mood, patient satisfaction, and end-of-life care. The primary results of this trial are detailed elsewhere.[22] The RCT was conducted at the University Medical Center Groningen among patients with newly diagnosed or recurrent lung cancer starting systemic treatment. Randomisation, data collection and management was performed by the Netherlands Comprehensive Cancer Organization. The study was approved by the institutional Medical Ethics Committee (NTR3540).

In short, patients were included within a week after start of systemic therapy and subsequently randomized in a 1:1 ratio to either the intervention group or the control group. Only patients assigned to the intervention group were invited to complete the DT and PL prior to their scheduled outpatient visit. Dependent on the DT-score, type of problems identified, and/or patient's referral wish, responses were discussed with a nurse practitioner specialized in psychosocial issues. Patients were subsequently offered referral to an appropriate and licensed professional (e.g. a psychologist, social worker, physical therapist, or a dietician). Patients assigned to the control group were not routinely screened for distress and did not complete the DT and PL. They received care as usual as determined by the treating clinician. The primary outcome was the mean change in the EORTC-QLQ-C30 global QoL-score between 1 and 25 weeks.

Study population

Between 1 January 2010 and 30 June 2013, 223 patients were enrolled in the trial (response rate 66%). All patients had received a histological diagnosis of any type of lung cancer (stage Ib through IV), had an Eastern Cooperative Oncology Group (ECOG) performance scale of 0, 1 or 2, had to start a form of systemic treatment, were without cognitive impairment, and were able to complete questionnaires in Dutch. Systemic treatment was defined as treatment with chemotherapy, adjuvant chemotherapy, chemo-radiotherapy, or treatment with biologicals. Of the patients included, 110 were randomized to the intervention arm. These patients were asked to complete the DT and were therefore included in the current analyses.

Patient characteristics and survival

Sociodemographic characteristics were obtained from the hospital's electronic health record at study entry as were clinical characteristics detailing on histological tumour type, performance

status, recurrent versus new diagnosis, disease stage, initial type of treatment, and the Charlson age-adjusted co-morbidity index were also derived from the electronic health record.[23] Date of death was recorded from the electronic health record up to one year after randomisation.

Distress Thermometer, Quality of Life, and mood

The DT is an extensively validated measure to screen for distress.[19,24,25] It consists of a single-item, visual analogue scale with a score ranging from 0 (no distress) to 10 (extreme distress) and is to be completed by the patient to quantify the level of distress experience in the past week. A score on the DT below either four or five, depending on the country and setting, has been propagated as optimal cut-off to rule out significant distress in patients with cancer.[19,26] An optimal cut-off value of five was observed among Dutch patients with cancer and therefore used in the current study. We did not use data obtained through the Dutch Problem List in these analyses.

All patients also completed the EORTC-QLQ-C30[27] to assess health-related QoL and the Hospital Anxiety and Depression Scale (HADS)[28] to assess mood. Scores on the EORTC-QLQ-C30 may range from 0 to 100 with higher scores reflecting better QoL. We only used the global QoL subscale in the current study as a best approximation to generic QoL. The HADS assesses symptoms of anxiety and depression over the past week with scores ranging from 0 (not at all) to 3 (very much). It consists of 14 questions and scores may vary from 0 to 21 with higher scores indicating more symptoms of anxiety or depression. All PROMs were completed after patients were randomised but within a week after the start of systemic therapy.

Selection of clinical predictors

Candidate predictors for one-year survival were selected based on the literature as well as expert opinion and availability of such predictors in clinical settings.[29–33] We selected the following five clinical or demographic predictors to be included in the model: 1) gender, 2) performance status (dichotomized as 0 or 1 versus 2), 3) disease stage (dichotomized as non-metastasized: stage I, II and IIIa versus metastasized: stage IIIb and IV) 4) the Charlson age-adjusted comorbidity index (entered as a continuous variable) and 5) tumour histology (dichotomized as non-small cell lung carcinoma versus small-cell lung carcinoma).

Statistical analyses

To characterize the study population, descriptive statistics were used to evaluate the frequencies, mean, and standard deviations for all sociodemographic and clinical characteristics as well as other study measures at study entry. Patients with significant distress (DT-score 5) were compared to those without significant distress (DT-score <5) using independent T-tests and Chi-square tests.[26] The one-year survival of patients with and without significant distress was

compared with the log-rank test and illustrated with a Kaplan-Meier curve. Statistical tests were performed with two-sided alternatives and considered significant if $P \leq 0.05$, using SPSS software version 25 and STATA/IC version 13.

Model building

Univariable Cox proportional hazard models were used to determine the association of these predictors separately with one-year survival. We examined the proportional hazards assumption using log-minus-log plots. Regardless of statistical significance, all selected predictors were subsequently entered together simultaneously into a Cox proportional hazard model. This constituted the basic model. Hereafter, we separately added three sets of PROMs to the basic model: 1) the DT-score; 2) the EORTC-QLQ-C30 global QoL score; and 3) the HADS total score. We report on the added value of these PROMS to the basic model by evaluating the change in -2 log likelihood (-2LL), the statistical significance, and Harrell's C-statistic with a 95% CI.[34] The - 2LL is a measure of accuracy or overall performance of the model whereas the C-statistic demonstrates the difference in discriminatory value of a model comparable to the area under the receiver operating characteristic curve.[34,35]

Reclassification of high-risk patients

To provide better clinical insight regarding the added value of the DT, we constructed a reclassification table including all patients who completed the DT. This table depicts the shift in classification of cases of mortality and non-cases separately for the basic model and the model after addition of the DT-score. To obtain this table, the individual survival risk was calculated for each patient using the baseline survival and the regression coefficients of the selected predictors. We then defined two risk groups (normal risk vs. high risk) primarily based on the net one-year survival date of patients with lung cancer. We defined the high risk group as patients having a one-year mortality risk as 85 percent.[36,37] This reclassification was not performed for models that included the EORTC-QLQ-C30 global QoL score or the HADS total score.

RESULTS

Study population

Relevant demographic and clinical characteristics of the included patients are displayed in Table 1. Approximately half of these patients was female (46%), 65% was diagnosed with stage IV lung cancer, and 81% was initially treated with a chemotherapy or chemo-radiotherapy regimen. A total of 97 patients (88%) accurately completed the DT. Patients not completing the DT (N=13) were comparable in all sociodemographic as well as clinical characteristics to patients who completed the DT (all p-values 0.10; data not shown).

TABLE 1. Description of total study population at study entry and comparison of groups with and without significant distress according to the Distress Thermometer

Characteristic	Total study population (N=110)	DT-score < 5 (N=46)[a]	DT-score 5 (N=51)[a]
Age (mean ± SD)	60.6 ± 10.5	59.8 ± 10.5	61.3 ± 10.7
Female sex (N [%])	50 (46)	20 (43)	24 (47)
Performance status (N [%])			
0	46 (42)	22 (48)	21 (41)
1	56 (51)	21 (46)	27 (53)
2	8 (7)	3 (6)	3 (6)
Recurrent disease, yes (N [%])	29 (26)	9 (20)	16 (31)
Disease stage (N [%])			
Stage 1 or 2	10 (9)	5 (11)	5 (10)
Stage 3	29 (26)	14 (30)	12 (23)
Stage 4	71 (65)	27 (59)	34 (67)
Smoking status (N [%])			
Yes	48 (44)	16 (35)	28 (55)
Quit	51 (46)	25 (54)	17 (33)
Never	11 (10)	5 (11)	6 (12)
Charlson age-adjusted comorbidity index (mean ± SD)	8.3 ± 2.4	7.9 ± 2.4	8.6 ± 2.5
Histology (N [%])			
Adenocarcinoma	64 (58)	25 (54)	31 (61)
Squamous cell carcinoma	19 (17)	8 (18)	9 (18)
Large cell n.o.s.	5 (5)	2 (4)	2 (4)
Small-cell carcinoma	20 (18)	10 (22)	8 (16)
Other	2 (2)	1 (2)	1 (1)
Initial type of treatment (N [%])			
Chemotherapy	60 (55)	22 (48)	32 (63)
Chemo-radiotherapy	29 (26)	15 (33)	11 (22)
Biological	21 (19)	9 (19)	8 (16)
EORTC-QLQ-C30 score[b, d] (mean ± SD)			51.5 ±
Global quality of life (N=94)	59.2 ± 20.8	69.4 ± 19.1	17.3***
HADS score (mean ± SD)[c, d]			
Anxiety subscale (N=93)	6.4 ± 4.1	5.1 ± 3.6	7.5 ± 4.2**
Depression subscale (N=93)	6.2 ± 3.9	4.9 ± 3.7	7.2 ± 3.6**
Total score (N=92)	12.6 ± 7.2	10.0 ± 6.3	14.6 ± 7.0**
Distress Thermometer (N=97)			
Score (median; range)	5.0 (0 – 10)	-	-
Score 5 (%)	46	-	-

Abbreviations: DT: Distress Thermometer, SD: Standard Deviation.

*p < 0.05, ** p < 0.01, ***P < 0.001, otherwise not significant (p>0.10)

a Patients below the DT-score cutoff and DT-score above cutoff were compared. The remaining 13 patients did not accurately complete the DT and could not be included in this analysis.

b The 30-item EORTC-QLQ-C30 assesses QOL. Scores can range from 0 to 100 with higher scores reflecting better functioning.

c The 14-item Hospital Anxiety and Depression Scale (HADS) assesses anxiety and depression levels over the last week in two subscales each consisting of seven items. Scores vary from 0 to 21 with higher scores indicating greater anxiety or depression.

d Number of respondents vary and are denoted per questionnaire or subscale

Comparison of patients with and without significant distress

Of the 97 patients who accurately completed the DT, 51 had a DT score ≥5 and 46 had a score <5. Patients with and without significant distress were comparable in terms of sociodemographic and illness-related characteristics (Table 1; all p-values 0.10). Patients with clinically relevant distress reported a significantly lower global QoL (p<0.001), and depicted higher scores on the depression and anxiety subscales of the HADS as well as the total HADS score (p=0.004; p=0.004; and p=0.001; respectively). Median one-year survival time (Figure 1) among patients with clinically relevant distress was significantly shorter: 7.6 months (95% CI: 6.5 – 8.7) versus 10.0 months (95% CI: 9.1 – 11.0; P=0.02).

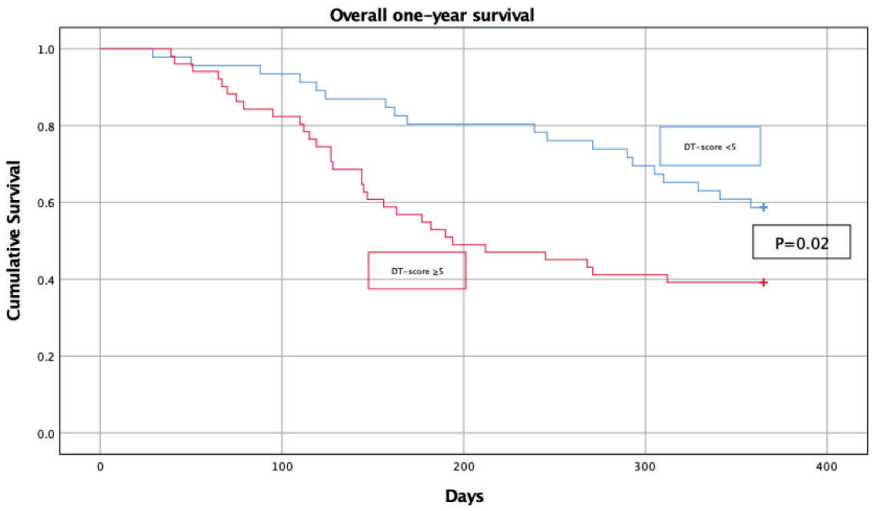

FIGURE 1. Kaplan-Meier overall one-year survival curve stratified by significantly elevated elevated distress as evaluated by the Distress Thermometer (cutoff score of 5). Survival data was calculated from the date of randomization and date of death was recorded up to one year later.

Univariable analyses and performance of multivariable models

Table 2 displays the univariable relationships between the five selected predictors and the three sets of PROMS with one-year survival. Performance status, disease stage, and the Charlson age-adjusted comorbidity index were all found to be significant predictors. Of the included PROMs, the global QoL-score and the DT-score were identified as significant predictors, but not the HADS.

TABLE 2. Univariable associations of selected clinical predictors with one-year survival

	Coefficient	HR (95% CI)	P-value
Clinical predictors			
Gender			
Male[a]	-	-	-
Female	-1.95	0.82 (0.49 – 1.38)	0.46
Performance status at inclusion			
0, 1[a]	-	-	-
2	1.43	4.18 (1.9 – 9.35)	0.001
Disease stage			
Stage Ib, II, IIIa[a]	-	-	-
Stage IIIb, IV	0.92	2.51 (1.14 – 5.53)	0.02
Charlson age-adjusted comorbidity index	0.23	1.26 (1.12 – 1.42)***	<0.001
Histology			
Non-small cell lung carcinoma[a]	-	-	-
Small-cell carcinoma	-0.25	0.78 (0.39 – 1.54)	0.47
Patient-reported outcome measures			
EORTC-QLQ-C30 score			
Global quality of life scale	-0.15	0.99 (0.97 – 1.0)	0.02
Hospital Anxiety and Depression scale			
Total score	0.013	1.01 (0.98 – 1.05)	0.32
Distress Thermometer			
Total score	0.21	1.24 (1.09 – 1.40)	0.001

a: Reference category
The Hazard Ratio is displayed per unit of the score for continuous variables.

Table 3 depicts the performance of the multivariable model as well as the performance of subsequent multivariable models when combined separately with the three sets of PROMs. The -2LL, i.e. the accuracy of the model, significantly improved after addition of the global QoL-score (491.4 to 431.9; P<0.001), addition of the HADS total score (491.4 to 410.0; P<0.001), and addition of the DT-score (491.4 to 397.5; P<0.001). The C-statistic, i.e. the discriminatory value, improved slightly from 0.69 (95% CI: 0.63 – 0.76) in the model with clinical predictors to 0.71 (95% CI: 0.64 – 0.77) after addition of the DT-score. Addition of the global QoL-score and the HADS total score led to a C-statistic of 0.69 (95% CI: 0.62 – 0.77) and 0.67 (95% CI: 0.60 – 0.75), respectively.

TABLE 3. Different multivariable models of selected predictors when combined with various patient-reported outcome measures

Variables included in model	-2 LL	P-value	C-statistic (95% CI)
Selected predictors (N=110)	491.4	-	0.69 (0.63 – 0.76)
Selected predictors + global Quality of Life (N=99)	431.9	<0.001	0.69 (0.62 – 0.77)
Selected predictors + symptoms of anxiety and depression (N=96)	410.0	<0.001	0.67 (0.60 – 0.75)
Selected predictors + Distress Thermometer score (N=97)	397.5	<0.001	0.71 (0.64 – 0.77)

P-value calculated (Chi-square two-sided test) versus model with selected predictors only Abbreviations: -2 LL: -2 Log Likelihood. C-statistic: Harrel's C concordance statistic

The five selected predictors: 1) gender, 2) performance status at inclusion, 3) disease stage, 4) Charlson age-adjusted comorbidity score, 5) histology.

Global Quality of Life was measured using the global QoL subscale of the EORTC-QLQ-C30. Symptoms of anxiety and depression were measured using the Hospital Anxiety and Depression Scale total score.

Improved reclassification of high risk patients

The reclassification model of the 97 patients of whom 50 died within one year is shown in Table 4. The proportion of correctly classified high-risk patients who died within one year increased from 8 percent to 28 percent (10 additional patients) after addition of the DT-score to the basic model. Moreover, addition of the DT-score did not considerably increase the proportion of patients incorrectly classified as high risk (Table 4; increase from 3% to 5%).

TABLE 4. Improved predicted one-year mortality risk classification with addition of the Distress Thermometer score to selected predictors among 97 patients with lung cancer

	Observed death within one year		
Predicted risk of mortality within one year	**Yes, N (%)**	**No, N (%)**	**Total**
Selected predictors			
Normal risk < 85%	46 (92)	46 (97)	92
High risk 85%	4 (8)	1 (3)	5
Total risk group	50 (100)	47 (100)	97
Selected clinical predictors + Distress Thermometer score			
Normal risk < 85%	36 (72)	45 (95)	81
High risk 85%	14 (28)	2 (5)	16
Total risk group	50 (100)	47 (100)	97

The five selected predictors: 1) gender, 2) performance status at inclusion, 3) disease stage, 4) Charlson age-adjusted comorbidity score, 5) histology.

DISCUSSION

To our knowledge, this is the first study to show that addition of a patient-reported distress score, as measured by DT, to clinical predictors may hold prognostic value when estimating one-year survival. Similar results were obtained when combining the selected predictors with QoL and symptoms of anxiety or depression. Further, patients with clinically relevant distress had a significantly shorter median one-year survival time when compared to patients without clinically relevant distress, whilst being comparable in terms of clinical and sociodemographic characteristics. This finding was also supported by the improvement in the classification of patients with a high risk of death (85%) after combining the DT-score with selected predictors. This suggests that addition of a patient-centered outcome that can be rapidly interpreted, such as the DT-score, allows clinicians to more accurately determine which patients are at risk for a poor prognosis and possibly personalize care accordingly.

When viewed in the light of current clinical practice, these findings are important for several reasons. First, we specifically opted to study the prognostic value of the DT since prognosis of patients with lung cancer is often poor and the overall one-year net survival is only 30 percent.[36,38] The DT was originally developed as a rapid screening and diagnostic tool to rule out clinically relevant distress in patients with cancer.[14,25] Studying the prognostic value of the DT may thus move this tool beyond the originally intended purpose. Yet, other PROMs such as QoL, anxiety, and depression have previously been identified as important prognostic indicators in multiple, large-scale studies.[8–11] More importantly perhaps, these outcomes are associated with distress.[39,40] Having a fast and efficient tool available that screens for distress, and simultaneously conveys prognostic information, is therefore a promising finding in this patient population.

Second, numerous studies conducted across different care settings have provided clear evidence to support the earlier integration of palliative care, sometimes even delivered concurrently with (curative) treatment.[41,42] This has led to an increased interest with regards to the earlier integration as well as official endorsement by clinical guidelines.[43] Yet, many patients with advanced (lung) cancer either receive such care at a late stage and the quality of this care can be improved.[44,45] Although the use of a short screening tool cannot substitute careful clinical assessment and management, routine use of the DT may aid clinicians in identifying those patients at risk for poor outcomes and provide a vantage point from which to earlier engage patients and caregivers in patient-centered conversations about advance care planning and palliative care options.

In contrast to our findings, one previously conducted study (N=113) did not identify the prognostic value of the DT in patients with stage III lung cancer treated with chemotherapy

containing carboplatin.[21] Notably, the observed median DT-score in that study was lower compared to the current study and the majority of patients refused to complete the DT and the associated Problem List. As described by the authors, this selection bias may account for the contrasting findings. Previous studies, although conducted among different cohorts of patients with advanced cancer, have shown that screening for distress has positive effects on the experienced of physical as well as psychosocial problems.[46,47] Moreover, these studies also observed that distress measures may convey important prognostic information in terms of survival.

A recent systematic review concluded that more effort is needed towards ensuring patients' adherence when completing PROMs and that routine completion should be supplemented by clear guidelines to support clinicians when discussing responses with patients.[12] Other PROMs such as QoL and anxiety or depression have been found to convey important prognostic information in patients with cancer.[9,11,16,48] Yet, these instruments are often lengthy and require additional training and time investment. Also, healthcare professionals have cited practical concerns related to the length of questionnaires and required time investment, disruption of workflow, costs, and a lack of training for accurate interpretation.[49] In contrast to this, the DT allows for rapid assessment and may therefore be easier to integrate in clinical settings.

Our findings should be viewed in light of certain limitations. The current study represents a secondary analysis of a previously conducted RCT at a single, academic institution and our sample size was small. Further, although we did include patients with any histological subtype of lung cancer and all patients started a form of systemic treatment, only patients with an ECOG performance status between 0 and 2 were eligible for inclusion in the trial (the full score ranges from 0 to 5). These observations limit the generalizability of our findings. Third, the current patient population does not include patients treated with immunotherapy. This recent treatment modality is likely to markedly shift the prognosis of patients with advanced lung cancer in the near future. It would therefore be interesting to investigate whether patients with increased levels of distress are also at risk of a poor prognosis among patients treated with immunotherapy.

Next, we used the -2LL and the C-statistic as a best approximation to general performance of the different multivariable models. The -2LL did show significant improvements after addition of the different PROMs but we did not observe similar findings using the C-statistic (all values between 0.67 and 0.71). The C-statistic, however, has been criticized for a lack of sensitivity with regards to recognizing the added value of a risk marker. It has therefore been recommended to additionally report a reclassification table since this conveys important complementary information.[50] In line with this, we decided to use a cutoff of 85 percent to define patients at high risk of dying within one year.[36,37] We specifically decided not to include

the EORTC-QLQ-C30 or the HADS in this reclassification table. Instead, we contrasted the performance of these PROMs in the outlined multivariable models to demonstrate similar performance of the DT when compared to other PROMs.

Although this cutoff likely represents the futility of further tumor-targeted treatment in this patient population, it was arbitrarily chosen and should be further validated in future studies. Last, the response rate in the original trial was relatively low (66%). This was most likely because of the high symptom burden these patients already face and was also stated as the most common reason for participation refusal (41% of objectors). This should be taken into consideration when interpreting our current findings.

In conclusion, this is the first study to provide evidence for added prognostic value of the DT-score in patients with lung cancer. The possible relationship between the DT-score and survival should be evaluated further in prospective, longitudinal studies across different settings and institutions.[9] Yet, our findings are promising and may allow clinicians to identify those patients at risk for poor outcomes and prevent discordance between care received and personal patient preferences near the end of life. This may further improve the timely delivery of high quality, patient-centered care for patients with lung cancer.

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V

Chapter 5

A qualitative study of serious illness conversations in patients with advanced cancer

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ABSTRACT

Background: Conversations with seriously ill patients about their values and goals have been associated with reduced distress, a better quality of life and goal-concordant care near the end of life. Yet, little is known about how such conversations are conducted.

Objective: To characterize the content of serious illness conversations and identify opportunities for improvement.

Design: Qualitative analysis of audio-recorded, serious illness conversations using an evidence-based guide and obtained through a cluster-randomized controlled trial in an outpatient oncology setting.

Setting/measurements: Clinicians assigned to the intervention arm received training to use the "Serious Illness Conversation Guide" to have a serious illness conversation about values and goals with advanced cancer patients. Conversations were de-identified, transcribed verbatim, and independently coded by two researchers. Key themes were analyzed.

Results: A total of 25 conversations conducted by 16 clinicians were evaluated. The median conversation duration was 14 minutes (range 4 – 37) with clinicians speaking half of the time. Thematic analyses demonstrated five key themes: 1) supportive dialogue between patients and clinicians; 2) patients' openness to discuss emotionally challenging topics; 3) patients' willingness to articulate preferences regarding life-sustaining treatments; 4) clinicians' difficulty in responding to emotional or ambiguous patient statements; 5) challenges in discussing prognosis.

Conclusions: Data from this exploratory study suggest that seriously ill patients are open to discussing values and goals with their clinician. Yet, clinicians may struggle when disclosing a time-based prognosis and in responding to patients' emotions. Such skills should be a focus for additional training for clinicians caring for seriously ill patients.

INTRODUCTION

People living with a serious illness may face added suffering due to poor communication, emotional distress, and discordance between the type of care desired and the care received.[1–4] Historically, completion of advance directives (AD) has been promoted as one way to ensure that patients receive the care that they want at the end of life.[5] However, advance directives have not proven to be consistently effective in achieving this.[6,7] Additionally, focusing on their completion may lead clinicians to limit conversations to medical procedures rather than discussing patient-centered values, goals and preferences.[5,8–11]

Therefore, experts increasingly emphasize the importance of discussing and recording patients' values and goals.[1,12,13] Research demonstrates the feasibility and benefit of such conversations, with positive effects on quality of life (QoL), distress, and goal-concordant care near the end of life.[14–17] Recommendations about best practices regarding such conversations include: understanding the patient's view of his/her illness, exploring information preferences, sharing prognostic information, understanding fears and goals, exploring views on trade-offs and impaired function as well as wishes for family involvement.[18] In addition, experts advocate the use of open-ended questions.[19–21] Yet, training clinicians to have these conversations and ensuring that such conversations are of sufficient quality remains an important challenge.[22,23]

Previous work has shown that patients value honesty, good listening skills, and humanity in their clinicians when talking about serious illness but also demonstrates that clinicians struggle when disclosing prognosis or discussing care options near the end of life.[24,25] Little is known about the details illustrating some of these challenges during such conversations.[26] We therefore analysed serious illness conversations, as informed by a structured conversation guide, between trained oncology clinicians and their patients in order to characterize the content and interactions of these conversations.

METHODS

Trial design and setting

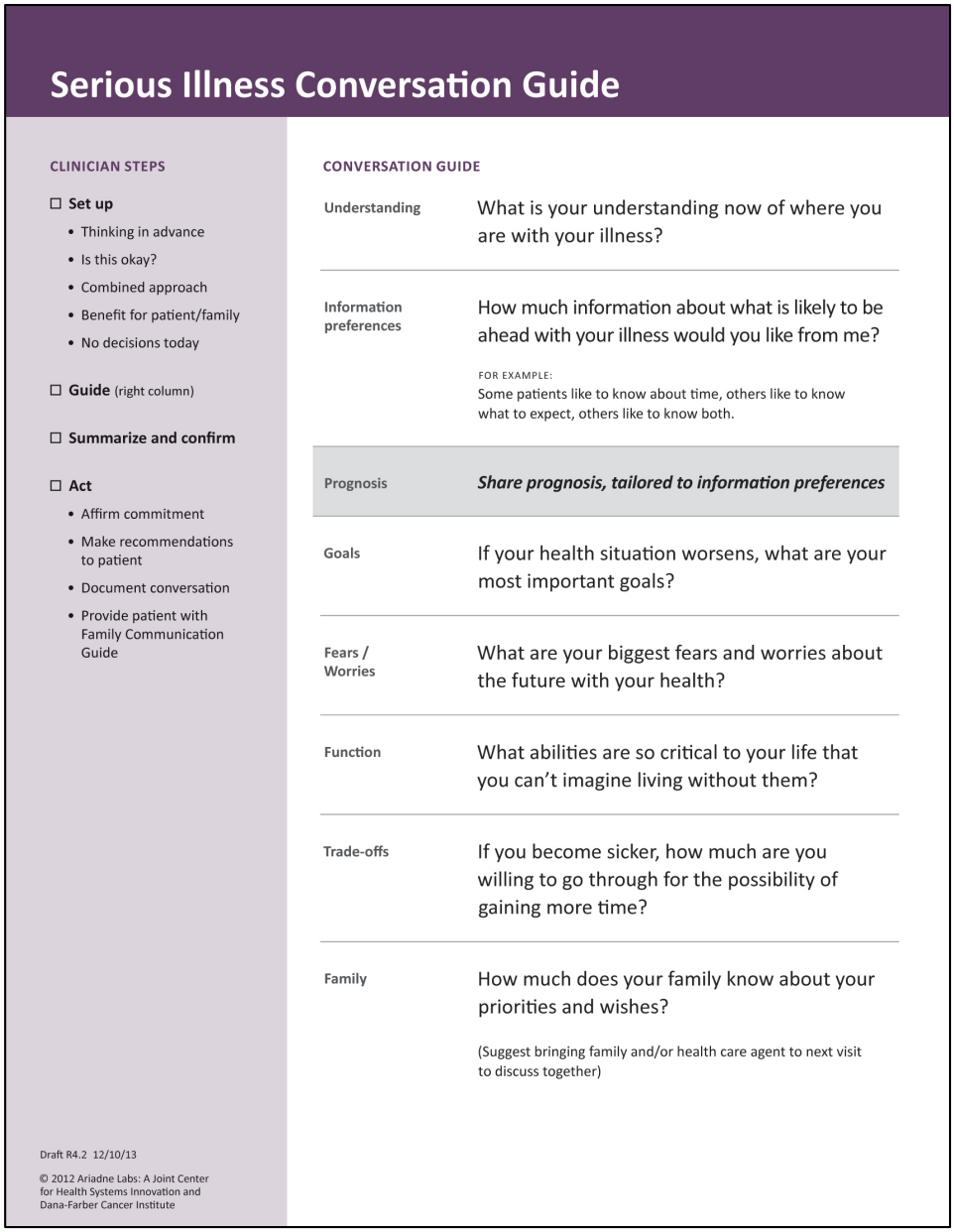
The Dana-Farber Serious Illness Communication trial has been previously described.[13] This cluster-randomized controlled trial assessed the impact of a multi-component, communication quality improvement intervention in an outpatient oncology setting. Only clinicians and patients assigned to the intervention arm of this trial were eligible for inclusion in the current study. The goal of this intervention was to move serious illness conversations to an earlier stage in the course of illness, in an outpatient setting, and with the patient's usual clinician. We defined a serious illness conversation as a type of advance care planning that focuses on values, goals, and preferences about future care between a clinician and a seriously ill patient. The trial and this study were approved by the Dana-Farber Cancer Institute (DFCI) Office for Human Research Studies (IRB).

The intervention consisted of tools, training, and system changes designed to support clinicians in having a serious illness conversation. Intervention clinicians (physicians, nurse practitioners or physician assistants) received a 2.5-hour skills-based training to use the "Serious Illness Conversation Guide." Clinicians then systematically used the surprise question (Would you be surprised if this patient died within the next year) to identify eligible patients with advanced cancer whom they believed were at risk of dying within one year.[27] Directly after the conversation, clinicians reported on the duration of the conversation. Control clinicians received no skills-based training or systems supports and were not provided with the SICG.

Serious Illness Conversation Guide

The SICG (Figure 1) is an evidence-based, clinician-facing framework for best communication practices.[13] It consists of eight components and supports clinicians in conducting patient-centered serious illness conversations, using open-ended questions and patient-tested language. This guide allows clinicians to explore a patient's view of his or her illness, information preferences, goals and fears, views on trade-offs and impaired function, and wishes for family involvement. This version of the SICG also suggests that clinicians tailor their time-based prognostic disclosure to a patient's individual information preferences.

The skills-based training included additional information, a role playing exercise, and explicit advice for clinicians to speak less than 50% of the time to support open-ended question use and successful patient engagement. In addition, clinicians were encouraged to follow the structure of the SICG, to respond to patient emotions and expressed concerns, and to de-emphasize decision making, so as to lessen anticipated anxiety for patients.



Serious Illness Conversation Guide

CLINICIAN STEPS

☐ **Set up**
- Thinking in advance
- Is this okay?
- Combined approach
- Benefit for patient/family
- No decisions today

☐ **Guide** (right column)

☐ **Summarize and confirm**

☐ **Act**
- Affirm commitment
- Make recommendations to patient
- Document conversation
- Provide patient with Family Communication Guide

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CONVERSATION GUIDE

Understanding	What is your understanding now of where you are with your illness?
Information preferences	How much information about what is likely to be ahead with your illness would you like from me? FOR EXAMPLE: Some patients like to know about time, others like to know what to expect, others like to know both.
Prognosis	***Share prognosis, tailored to information preferences***
Goals	If your health situation worsens, what are your most important goals?
Fears / Worries	What are your biggest fears and worries about the future with your health?
Function	What abilities are so critical to your life that you can't imagine living without them?
Trade-offs	If you become sicker, how much are you willing to go through for the possibility of gaining more time?
Family	How much does your family know about your priorities and wishes? (Suggest bringing family and/or health care agent to next visit to discuss together)

FIGURE 1. The Serious Illness Conversation Guide

Qualitative study sample

Patients eligible for inclusion in the trial were 18 years or older, received their oncology care at DFCI, spoke English, and were without cognitive impairment. Full inclusion and exclusion criteria are described elsewhere.[13] Clinical and demographic characteristics of these clinicians and patients were compared to the intervention arm of the trial. Family members were allowed to be present during the conversation.

All serious illness conversations between randomized intervention clinicians (N=48) and patients (N=134) were eligible for audio-recording. We initially approached one out of every four clinician-patient dyads. Using this approach, our response rate was low and we subsequently decided to approach every dyad. Dyas were approached by enquiring directly after randomization whether their conversation could be audio-recorded. Informed consent was obtained and obtained again directly prior to the conversation. In addition, all patients with metastatic melanoma, as well as clinicians caring for these patients, were approached, even though they were excluded from the trial (because they served as a pilot site). Since these clinicians had received the same skills-based training as the remainder of the intervention group we included them in the current analysis. In total, we obtained and included 25 conversations (19% of all possible conversations), conducted by 16 clinicians.

Data analysis

A multi-disciplinary research team with expertise in psychiatry, palliative medicine, pulmonary and critical care medicine, oncology and qualitative methods developed and iteratively revised a preliminary coding scheme based on the content and flow of the SICG. This coding scheme also included codes to capture particular aspects of these conversations (e.g. discussions revolving around life-sustaining treatments). A subset of codes detailing on the patient-clinician relationship were also included in the coding scheme (e.g. positive affirmation or ambivalence). The set-up of the conversation was not included in the analysis. A subset of four randomly selected transcripts were read and coded using this preliminary coding scheme and, throughout this iterative process, new codes were added to reflect newly emergent themes. Trustworthiness of the data analysis was ensured through having two independent coders, a senior experienced clinician with expertise in palliative medicine and psychiatry as well as an expert on qualitative research methodology. Dependability was further ensured through the iterative development of a coding scheme capturing various aspects of the conversation. Conformability of the findings was ensured by not having any research staff present during the conversations.

Two independent researchers (DJL and OPG) subsequently coded each transcript. Neither of these researchers had an established relationship with the study clinicians or patients. Because

of the exploratory nature of the study, an inductive coding approach was used and additional emerging themes or codes could be added throughout the coding process. Disagreements were first discussed among the two researchers and, if needed, resolved through a verbal consensus discussion with a third, independent researcher (SDB). Coding was performed using the NVivo 11 Pro (QSR International) qualitative data analysis software and we adhered to the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist.[28] We assessed the percentage of words spoken by clinicians using a word count. This is a relatively crude estimation of the percentage of time spoken by each interlocutor and does not account for silences or other important forms of nonverbal communication throughout these interactions. Last, clinicians also reported on the duration of the conversation directly afterwards. This estimation was used to calculate the median duration of the conversations.

RESULTS

Patient and clinician sample

Table 1 describes demographic and clinical characteristics of the patient sample (n=25). Their mean age was 60.3 years (95% CI: 54.3 – 66.5*),* 48% were female, all were white, and 48% of patients described their health as: *Relatively healthy and terminally ill*.

TABLE 1. Characteristics of Patients in the Qualitative Study Sample

Characteristic	Qualitative study sample (n=25)
Age in years - mean (95% CI)	60.4 (54.3 – 66.5)
Female sex – N(%)	12 (48)
Race - N(%)	
White	24 (96)
Black or African American	0 (0)
Other	0 (0)
Missing	1 (4)
Hispanic – N(%)	0 (0)
Missing	1 (4)
Married/partnered – N(%)	19 (76)
Missing	1 (4)
Income >$75,000 – N(%)	15 (60)
Missing	3 (12)
Disease center - N(%)	
Breast oncology	
Gastrointestinal, Genitourinary, Head & Neck,	6 (24)
Neurology, Sarcoma, Thoracic, other	14 (56)
Hematologic Malignancies, Lymphoma	0 (0)
Melanoma[a]	5 (20)
Health insurance type - N(%)	
Medicare	6 (24)
Medicaid/Mass Health	3 (12)
Private	13 (52)
No insurance	0 (0)
Other	0 (0)
Missing	3 (12)
Patient-reported health status - N(%)	
Relatively healthy and not seriously ill	7 (28)
Relatively healthy and terminally ill	12 (48)
Seriously but not terminally ill	5 (20)
Seriously and terminally ill	1 (4)
College, graduate or professional school – N(%)	21 (84)

a These patients were part of a pilot trial and not included in the trial sample

Table 2 describes demographic characteristics of the clinician sample (n=16). Of these, fifty percent were female, most were physicians (69%), and physicians had an average 13.9 years of attending-level clinical experience. Characteristics of both patients and clinicians were compared to the remainder of the trial populations. This analysis revealed no statistically significant differences (data not shown) except for a lower percentage of patients insured through Medicare in the qualitative study sample (24% vs. 49%; $p<0.05$).

TABLE 2. Characteristics of clinicians in the qualitative study sample

Characteristic	Qualitative study sample n=16
Female sex - n(%)	8 (50)
Discipline - n(%)[a]	
Physician	11 (69)
Nurse practitioner	4 (25)
Physician assistant	1 (6)
Disease center - n(%)	
Breast oncology	
Gastrointestinal, Genitourinary, Head & Neck,	4 (25)
Neurology, Sarcoma, Thoracic, other	8 (50)
Hematologic Malignancies, Lymphoma	0 (0)
Melanoma[a]	4 (25)
Years in clinical practice - mean (95% CI)	13.9 (7.0 – 20.7)

Description of conversations

A nurse practitioner or physician assistant conducted six conversations (24%) and physicians conducted the remainder. The median audio-recorded duration of conversations was 14 minutes (range 4 – 37). On average, clincians spoke 53% of the time (range 26% – 70%) and 48% of clinicians directly asked the patient about any additional questions the patient had.

The final codebook contained 39 codes spanning seven topics (Supplementary table A). Our analysis revealed five key themes: 1) supportive dialogue between patients and clinicians; 2) patients' openness to discuss emotionally challenging topics with their clinicians; 3) patients' willingness to articulate preferences regarding life-sustaining treatments; 4) clinicians' difficulty in responding to emotional or ambiguous patient statements; 5) challenges in discussing prognosis. We obtained data saturation after approximately 22 conversations.

Supportive dialogue between patients and clinicians

Throughout most conversations, clinicians were quick to offer positive affirmation and demonstrated strong rapport with their patients by referring to their history together, joking, and asking questions about other family members:

> *Clinician: Yeah, well you have a terrific attitude, and it's definitely impacted how well you've done over the past five years.*
> *[Clinician #12]*

Elements of such dialogue were also reflected through clinician reassurances, particularly as they pertained to talking with family members or other loved ones about disease status or progression. In most conversations, clinicians also reassured their patients and caregivers that patients would be kept as comfortable as possible throughout the disease process:

> *Clinician: Well, in terms of being in a lot of pain, we are sort of responsible for making sure that that becomes controlled. That we control that pain for you. And, and my job is to make sure that first of all, you know, you're safe. That's my biggest concern.*
> *[Clincian #7]*

Although the language use and general tone of the conversations was interpreted as supportive dialogue, clinicians did not always adequately respond to emotional or ambiguous patient statements.

Patients' openness to discuss emotionally challenging topics

In the majority of conversations, patients offered open, personal and direct responses to both questions of the SICG and clarifying questions beyond:

> *Clinician: … if your health situation worsens, what are your most important goals?*
> *Patient: That I don't make a fool of myself. That I handle it with dignity….You know, accept it, deal with it as best you can. Clinician: Have you found it difficult to accept?*
> *Patient: No, so far I've done it with some grace and good humor.*
> *[Clinician #13; Patient #20]*

Only in one case did a patient specifically decline to answer a question by requesting a "pass." Patients introduced the words "death" and "dying" more frequently than their clinicians, often in the context of talking about their fears (*Umm…my biggest fear is, is dying. You know, basically, leaving my kids and my wife behind; Patient #22)*, or when describing their illness understanding. When asked about their most important goals, the majority of patients were realistic (*You know, I'm not looking to climb Mt. Everest at this point; Patient #20)*. Most patients articulated the importance of being at home with family, making sure loved ones were provided for and not burdening others emotionally or financially:

> *Clinician: Do you have specific goals that you want to achieve?*
> *Patient: Just to spend time with the family. That's about it, you know. Uh, and be here as long as I can. I'm not looking for a miracle. I'm just looking for a little time.*
> *[Clinician #15; Patient #24]*

Patients' willingness to articulate preferences regarding life-sustaining treatments

Preferences regarding life-sustaining treatments were discussed in most conversations (76%) although the SICG does not specifically address this. Of these 19 conversations, the topic was initiated more frequently by the patient rather than by the clinician. The majority of patients expressed a clear preference against the use of life-sustaining treatments:

> *Patient: I am not to be resuscitated… if I die, let me die.*
> *[Patient #13].*

When articulating their specific preferences for or against such treatments, patients usually did so in response to the tradeoffs question: "*If you become sicker, how much are you willing to go through for the possibility of gaining more time?"* Patients also frequently used anecdotes related to past, personal experiences to justify such preferences:

> *Patient: I had somebody that I worked with and he had a massive stroke, and he can't do anything. Can't move, can't speak, you know, can blink his eyes, that's it. I don't think I'd want to… I wouldn't want to live like that.*
> *[Patient #4]*

In response, several clinicians dissuaded the patient from making any decisions regarding the use of life-sustaining treatments at this time because their health status was too good or because preferences change and patients might feel differently in the future:

> *Clinician: This is not anything permanent right now that we're talking about.*
> *Patient: Right.*
> *Interviewer: This is more kind of to get the ball rolling…*
> *Patient: Yeah.*
> *Clinician: And you're in such wonderful health now!*
> *[Clinician #8; Patient #13]*

> *Clinician: Because I think you're actually healthy enough that... as an otherwise healthy, what, sixty-seven year old? I don't know. So why don't you think about that and next time you come back we can talk about it again.*
> *[Clinician #9]*

Further, among the patients who expressed their preferences regarding life-sustaining treatment, only one was encouraged to complete an advance directive or similar legal documents.

Clinicians' difficulty in responding to emotional or ambiguous statements

In the majority of conversations, patients explicitly stated that they understood their disease to be incurable. Several patients however, did articulate their hope for a cure or described that they thought their disease was in remission. In some of these cases, clinicians attempted to reframe a patient's expectations:

> *Patient: Well, it's, it's, in, I guess it's in remission. Which is good news. So, that's as much as I know.*
> *Clinician: Well, I think remission might be the wrong word.*
> *Patient: The wrong word. It's "holding steady", I probably should've said*
> *[Patient #14]*

In other conversations, rather than exploring or reframing their patient's (mis)understanding, clinicians expressed optimism or did not follow-up on such statements:

> *Patient: How I'm progressing, is it pretty…it's pretty standard? Clinician: Oh no. You're doing outstanding. You're outstanding. You're doing great!*
> *[Clinician #4; Patient #6].*

Patients frequently expressed emotions or alluded to the struggles of facing a serious illness. Such statements, either implicitly or explicitly, revealed patients' unmet informational needs, emotional distress, or uncertainty about their current or future health status, quality of life, or treatment. Clinicians' responses were frequently limited to "*Okay*" or "*Uh huh*" or clinicians did not explore such statements further:

> *Clinician: We'll mostly focus today on, you're in great shape!*
> *Patient: Right.*
> *Clinician: How can we keep you in great shape?*
> *Patient: So, I've been thinking of the other, inevitable, as well…*
> *Clinician: Okay, good. [Clinician moves on]*
> *[Clinician #3; Patient #5]*
> *Patient: Quality of life is much more important to me than longevity.*
> *Clinician: Okay.*
> *Patient: I want both.*
> *Clinician: I know… and we're working to give you that… but um…*
> *Patient: I know that… I know that.*
> *[Clinician #1; Patient #1].*

Challenges in discussing prognosis

Out of the 25 conversations, two patients explicitly stated that they did not want to receive any information about what was likely to be ahead with their disease as illustrated below:

> *Patient: Personally I like taking things a step at a time. So, I guess my feeling is that I don't like to be projecting too far ahead. I realize the outcome probably will be grim at some point. But I think the business of working with it as it it is is, at least in my mind, satisfying. [Patient #18]*

All other patients either wanted to be fully informed (72%) or receive some information but not all (20%). Subsequently, clinicians disclosed prognosis, as recommended in the SICG and reinforced in the skills-based training, in 10 of the conversations. When broaching the topic of prognosis, both clinicians and patients often expressed a need for optimism. Of those clinicians who provided a prognosis, only three provided a time-based estimate of prognosis (e.g. how long the patient is expected to live). Instead, clinicians commonly focused on future treatment options, often in relatively lengthy monologues containing highly medical language:

> *Clinician: Then there are subgroups of patients, and then one of the subgroups that has a better and more favorable prognosis are those patients with the EGFR mutations and so, and we do know that their, their median survivals in places like here… those are the people we now hope our patients can be. And then there are some patients that have those much more slowly growing cancers, and then we don't know whether you're going to fit into that fourth category in terms of a response [...] We've seen the metastases to the brain and so that's telling us that it's probably not one of those very, kind of indolent lung cancers. It's been in the lungs for many, many years, but we don't know, yet, because you haven't had the EGFR inhibitor, whether you're gonna be one of the group that can have a more prolonged response to those kind of certain things.*
> *[Clinician #10]*

In other cases, clinicians described an uncertain prognosis, characterized by disease that could remain stable, other medical problems that could ensue, or details on how the cancer could suddenly progress and lead to complications. The likelihood of various trajectories, however, was often not addressed:

> *Clinician: The scan today, compared with the one from four months ago, shows very little change, and, that's great, it is possible that you could be alive for years in this state. In this current state is it possible something bad could happen – could it spread to another site, you know, the brain? Similar to that, a bleeding into the tumor, or, small vessel rupture related to*

the tumor, those things could happen. It could take your life, you know, much more rapidly? But of course, people of your age could have a stroke, as well. These things could happen, also, independent of your cancer. [Clinician #7; Patient #11; Age 77]

Finally, a minority of clinicians, although articulating that the disease was indeed incurable, used ambivalent and confusing language to do so:

Clinician: No, it's good. I mean, you do have stage 4 disease, that's never gonna change.
Patient: Right.
Clinician: But after you had that surgery recently… that rendered you disease-free.
Patient: Right.
Clinician: So, your stage 4 is no evidence of disease.
[Clinician #8; Patient #13]

DISCUSSION

The aim of the current study was to provide a descriptive overview of serious illness conversations conducted using a structured conversation guide. Our analysis of 25 audio-recorded and guide-led serious illness conversations between oncology clinicians and patients with advanced cancer revealed several insights. First among these is the warmth and comfort of patient-clinician relationships. Clinicians in our sample provided space for patient-centered conversation and focused on what was important to patients, as supported by the finding that clinicians spoke approximately half of the time. Further, their patients appeared to be open to discussing emotionally challenging topics and usually had clear preferences regarding their future care. Previous literature has suggested that similar conversations either do not take place, happen late in the disease course, or focus primarily on symptom control and preferences regarding life-sustaining treatments, while failing to adequately address patients' personal values and goals.[9,29–31] We found that training and a systematic framework allows clinicians to engage in these challenging conversations, provides space for patients to express their thoughts and feelings, and explores basic values and QoL-issues while engaging patients in planning for the future.

Yet, we also demonstrated that clinicians, in spite (or because) of their warm and comfortable relationships with their their patients, frequently did not meet this standard, especially when discussing prognosis. Emotional discomfort on part of both the clinician and patient is likely to contribute to this pattern. Moreover, clinicians sporadically followed up with patients about their expressed preferences regarding life-sustaining treatments. Discussing the future with seriously ill patients can be an emotional experience, and often elicits anxiety, sadness, and

fear.[3,9,32,33] Because clinicians experience strong positive feelings for their patients, they too may experience distress when discussing these issues.[34,35] Clinicians' emotional discomfort may manifest as avoidance, ignoring the patient's concerns, or excessive optimism.[36,37] Although clinicians may avoid these discussions to be kind or protective, such avoidance may lead patients to feel isolated with their concerns, or contribute to care that misaligns with patient preferences.[34]

Further, we observed a prognostic discussion in approximately half of the conversations and few clinicians provided patients with a time-based estimate (12%) even though the skills-based training suggested that clinicians tailor their prognostic disclosure to individual patient preferences. Instead, clinicians primarily focused on treatment options or discussed prognosis indirectly. Previous, predominantly quantitative research, has shown that clinicians regularly fall into one of the following pitfalls when communicating a patients' prognosis: excessive optimism, a focus on medical treatments without conveying a specific time-estimate, or the use of vague language to avoid distress in patients or caregivers.[26,38,39] These behaviors may reflect previous findings that over 70% of medical oncologists report inadequate or no communication training on prognostic disclosure and 88% feel ill-requipped to conduct these conversations.[38] Nonetheless, nearly all (96%) do believe it should be part of their training.[40,41]

Discussing prognosis with patients does not appear to be intrinsically harmful to the patient-clinician relationship and may even strengthen therapeutic alliance.[42] Although not a new observation,[43,44] this suggests disclosing a time-based prognosis may be challenging and might lead us to think about different ways to train clinicians (e.g. by framing prognosis as a worry about functional decline or concerns about an unlikely, but possible rapid deterioration without time for future planning). Such ways could allow clinicians to better tailor the type of prognostic disclosure used to individual patient preferences. In addition, clinician need training in specific communication competencies focused on: 1) titrating difficult information to in-the-moment observations of the patient's emotional responses to avoid burdening patients with emotionally-overwhelming information that can be more than desired, or for which the patient is not ready[45] and 2) discussing uncertainty in ways that acknowledges realities and supports appropriate hope. We think of both of these key clinical competencies as "gentle directness".

Our findings should be viewed in light of a self-selection bias since both patients and clinicians had to consent twice before the audio-recording of the conversations. It is thus likely that patients in this sub-sample may have been more comfortable talking about these issues than other patients and were well prepared by the consent process to have the conversation. We also assume that clinicians who consented to be audio-recorded might be more comfortable than those who did not; the behavior we observed here may therefore be a relatively positive

representation of how clinicians conduct such conversations. In this analysis, the lack of a control group in which clinicians were not trained and did not use the SICG precludes conclusions about how conversations may have been similar or different without the intervention. Furthermore, patients were drawn from a single institution, predominantly highly educated and white. Cultural or racial factors are important during these interactions[46,47] but could not be adequately explored in the current study.

Despite these limitations, this study has several strengths. Our analysis resulted in thematic saturation before we had analyzed 25 conversations thereby making it unlikely that we missed key themes.[48] Further, although we were unable to capture nonverbal communication through video, these audio-recordings provide a great deal of information about what happens in a real clinical encounter. All clinicians in this study received the same skills training, and most adhered to the systematic structure of the SICG. This allowed us to compare a group of relatively homogeneous conversations and to more closely examine variations in how the conversation topics were handled by the clinicians and patients.[49]

If our findings are supported by further research, they suggest several pathways to improving care. Patients generally expect their clinicians to initiate serious illness discussions[38]. Although some clinicians fear that these conversations might "take away hope" or be distressing for patients,[24] patients in our study responded positively to the questions in the SICG and frequently initiated conversation about difficult and personal topics. If clinicians ask appropriate, open-ended questions, patients may perceive that their clinicians are more open to other patient-initiated conversation, and be more willing to bring up their concerns and preferences.

In conclusion, the clinicians and seriously ill patients in our study were receptive to, and engaged by, conversations in an outpatient setting using a structured framework. Moreover, the quality of these conversations is aligned with expert recommendations to use open-ended questions, focus on basic values and goals, and for clinicians to speak no more than half the time. Yet, even when clinician-patient relationships are strong and conversations adhere to these standards, clinicians still experienced challenges in sharing prognostic information aligned with patient preferences, addressing emotions, clarifying concerns and preferences, and in following up on treatment limitations. Further research to better understand the mechanisms behind such challenges may enable clinicians to evolve such skills and help develop new approaches to deliver high-quality, serious illness care.

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SUPPLEMENTS

SUPPLEMENTARY TABLE A. Coding scheme

Illness understanding & Information preferences	
Prognosis	Discussion revolving around prognosis or prognostic disclosure
Information preferences	Discussion on information preferences regarding the disease
All information	Patient wants all information regarding his or her disease
Limited information	Patient wants limited information or no information regarding his or her disease
Illness understanding	Discussion on a patients' understanding of illness
Preparedness or acceptance / existential talk	Discussion on being prepared for the future course of illness or having accepted the future
Death	Specific mention of death (both exact and non-exact)
Goals & trade-offs	
Quality of life	Explicit statements on quality of life
Trade-offs	Discussion on what a patient is willing to go through in order to have more time
Goals	Discussion of any (treatment) goal except for quality of life (separate code)
Abilities & function	
Abilities or functions	Preferably use sub code
Concerns	Concern about abilities or functions
Preferences	Preference about abilities or functions
Symptoms	Preferably use sub code
Concerns	Concern about cancer- or treatment-related symptoms
Preferences	Preference about cancer- or treatment-related symptoms
Family or friends	
Family or friends	Discussion regarding family or friends in the broadest sense: awareness of family, involvement concerns and concerns of family
Emotions	
Hope	Expressing feelings of hope
Happiness	Expressing feelings of happiness or joy
Fear	Expressing current or future fears
Worry	Expressing current or future worries
Anger / frustration	Expressing feelings of anger

SUPPLEMENTARY TABLE A. Continued

Sadness	Expressing feelings of sadness
Loneliness	Expressing feelings of loneliness
Uncertainty	Expressing feelings of uncertainty
Self-doubt	Expressing feelings of doubt or self-doubt
Patient / clinician relationship	
Clinician discomfort / struggle	Discussion from which discomfort or struggle by clinicians become apparent
Decision making	Discussion on decision-making regarding treatment
Reassurance	Clinician providing a form of reassurance
Explanation or clarification	Clinician providing an explanation or clarification
Recommendation	Recommendation made by the clinician
Statement of understanding	Statement of understanding made by the clinician
Positive affirmation	Form of positive affirmation offered by the clinician
Humor / expressions of humor	Expression of humor as part of the conversation
Reset of expectations	Preferably use sub code
Positive	Positive way of resetting a patients' expectations
Negative	Negative way of resetting patients' expectations
Important anecdote	Anecdote expressed by a patient regarding important experiences or life events
Ambivalence	Discussion or statement reflecting ambivalence by either the clinician or the patient
Positive developments	Description of positive developments after a cancer diagnosis
Practical issues	
Financial	Discussion regarding financial issues
Hospice, bridge to hospice, death Religion / spirituality	Discussion on hospice, bridge to hospice, or place of death Discussion on religion or spirituality
Role of hospital / healthcare workers	Discussion on quality of the provided hospital services or healthcare professionals
Practical issues / documentation	Mention of practical aspects (planning) or documentation of EOL issues
Cancer treatment	Discussion on forms of treatment directly related to treating the cancer
Life-sustaining treatment	Discussion on forms of life-sustaining treatments

VI

Chapter 6

Concordance between serious illness conversations and clinician documentation among patients with advanced cancer

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ABSTRACT

Purpose: Serious illness conversations are part of advance care planning and focus on prognosis, values and goals. To be maximally effective, such conversations must be documented accurately and be easily accessible. We rated concordance between serious illness conversations using an eight-element guide and clinician documentation. We also assessed clinician adherence (fidelity) to the guide.

Methods: Data were obtained as part of a trial in patients with advanced cancer. Clinicians were trained to use a guide to conduct and document serious illness conversations. Two researchers independently compared audio-recordings with corresponding documentation in an electronic health record (EHR) template and free text progress notes and rated the degree of concordance.

Results: We reviewed a total of 25 audio-recordings. Clinicians addressed 87% of the conversation guide elements. Prognosis was discussed least frequently, only in 55% of the patients who wanted that information. Documentation was fully concordant with the conversation 43% of the time. Concordance was best when documenting family matters and goals and most frequently erroneous when documenting prognostic communication. Most conversations (64%) were documented in the template, a minority (28%) only in progress notes and two conversations (8%) were not documented. Concordance was better when the template was used (62% vs. 28%).

Conclusion: Clinicians adhered strongly to the conversation guide. However, key information elicited was documented and fully concordant less than half the time. Greater concordance was observed when clinicians used a pre-specified template. The combined use of a guide and EHR templates holds promise for advance care planning conversations.

INTRODUCTION

Advance care planning (ACP) can help patients with a serious illness to receive care consistent with their wishes and priorities.[1–3] Recent research has demonstrated that timely, high-quality communication between patients and clinicians is associated with improved quality of life, earlier use of hospice services and improved family bereavement outcomes.[4,5] In our fragmented healthcare system, the electronic health record (EHR) is an essential communication vehicle for conveying patients' preferences to the many clinicians providing care across different settings. In an emergency, both clear and accurate, as well as accessible ACP documentation can make a critical difference in care quality.[6] However, research has shown that clinicians often struggle to find key components of advance care plans in the EHR.[7] A growing number of institutions have thus initiated quality improvement projects to improve ACP documentation in their HER.[8] These include automated prompts, electronic order sets, or templates specifically designed to document key elements of ACP including patient values and individual goals.[8]

The extent to which clinicians address the key components of high-quality advance care planning conversations, and document them accurately largely remains unexplored. We used audio-recordings of clinician-led conversations using a The Serious Illness Conversation Guide (CIT), an evidence-based, validated structure for conversations about goals, values and preference, to evaluate adherence to recommended elements, and then compared documentation of conversations using the Guide with the corresponding clinician documentation in the EHR, both in a template and in free text progress notes.[9,10] The goals of the current study were: 1) To assess clinician adherence (fidelity) to the conversation guide; and 2) To compare the concordance between the substance of the audio-recorded conversation and the documentation in the EHR.

METHODS

Trial design and setting

We conducted a secondary analysis of data obtained through a cluster-randomized controlled trial of a communication quality-improvement intervention: the Serious Illness Care Program.[9] The trial was conducted in the outpatient oncology clinics at Dana-Farber Cancer Institute (DFCI) and approved by the Institutional Review Board. The goal of this intervention was to support the patient's primary oncology clinician in conducting ACP conversations with advanced cancer outpatients, using a set of tools, training, and systems change interventions.[9] Tools included the SICG as well as supporting documents to help patients both prepare for and continue ACP conversations at home.

The SICG contains eight conversational components: Illness understanding, information preferences, prognostic communication, goals, fears/worries, function, tradeoffs, and family. Intervention-arm clinicians (physicians, nurse practitioners or physician assistants) received a 2.5-hour skills-based training to use this conversation guide. Systems change interventions included systematic patient identification, reminders to conduct conversations, and an EHR template.

The EHR template

The EHR template consisted of dropdown menus and free text options for each component to support and structure clinician documentation of responses to the SICG (Supplementary Table A). The template served as a mechanism to document patients' responses and was not a medical order.

Study sample

All serious illness conversations between clinicians (N=48) and patients (N=134) assigned to the intervention arm of the trial were eligible for audio-recording. Study staff initially approached one out of every four clinician-patient dyads. However, because the response rate was low using this approach, the protocol was changed to allow investigators to approach every dyad. Clinicians and patients were asked directly after randomization whether their conversation could be audio-recorded, and informed consent was obtained again prior to the conversation. Patients with metastatic melanoma and their clinicians were also eligible for audio-recording but were excluded from the trial because they served as a pilot site. Since these clinicians had received the same skills-based training as the remainder of the intervention group, we included them in this analysis.

Since clinicians assigned to the control arm did not receive specific instructions on how or where to document, and because their conversations were not audio-recorded, we did not include their EHR data in the current study. Twenty-five analyzable ACP conversations, conducted by 16 clinicians, were obtained. Clinical and demographic characteristics of this census sample of clinicians and patients were compared to the rest of the clinicians in the intervention arm of the trial. These conversations were transcribed verbatim and de-identified.

Analysis

To ensure trustworthiness of our categorizations, two researchers (DJL and OPG) independently read each transcript and subsequently all corresponding clinician documentation. The researchers resolved coding differences by consensus, or when necessary, with the assistance of a third investigator blinded to their responses (SDB). Because the clinicians had been trained to follow a structured guide, we identified all conversation components in the guide and systematically recorded which topics in the guide were not discussed. The category "*Not discussed"* was used to identify elements of the conversation guide that were skipped entirely and provide an indicator of fidelity to the conversation guide. Of those topics that were discussed, researchers then rated the concordance of the documentation compared to the audio-recorded conversation by answering the question: *Does the documentation accurately reflect the key elements of what the patient said during the conversation?*

Using this prompt, researchers rated the documented response to each of the eight components as either one of the following four categories: *Concordant* (information is present and accurate*)*; *Partially concordant* (information is present but incomplete); *Not concordant* (information is elicited but inaccurate information is documented or information is documented but not discussed*); Not documented* (information elicited, but no information documented).

These responses were used to categorize all available information and assess overall concordance across all SICG components. Data elements were determined to be accurate if they documented the themes and statements patients made in response to the related component of the SICG. Overall concordance was calculated using the total number of conversational components that were discussed across all conversations (e.g. had they all been discussed, the eight conversational components across 25 conversations would have led to 200 potential components across all conversations). Finally, conversation-documentation concordance was examined separately in the template and the progress note.

RESULTS

Clinician population and documentation

Table 2 displays the characteristics of the 16 clinicians included in our sample compared to clinicians in the remaining study sample. Of note, half of the clinicians were female and their average number of years in clinical practice was 13.8 (95% CI 7.0 – 20.7). All characteristics were comparable with the exception of disease center since clinicians caring for patients with metastatic melanoma were also eligible for inclusion in the current study. These clinicians were similar to the clinicians caring for patients from different disease centers (data not shown).

In the 25 sets of audio-recorded conversations and corresponding documentation, clinicians used the template across 16 conversations (64%) and only documented using the progress note in seven conversations (28%). We did not identify any documentation in either the progress note or the template for the remaining two conversations (8%). Thus, documentation was only available on 23 conversations. Examples of template and progress note documentation are presented in Table 3 along with the component of the ACP conversation and rated concordance.

TABLE 2: Clinician sample compared to the remainder overall study sample of clinicians

Characteristic	Qualitative study sample n=16	Remainder overall study sample n = 79
Female sex - n(%)	8 (50)	46 (58)
Discipline - n(%)[a]		
Physician	12 (75)	57 (72)
Nurse practitioner	3 (19)	19 (24)
Physician assistant	1 (6)	3 (4)
Disease center - n(%)		
Breast oncology	4 (25)	17 (22)
Gastrointestinal, Genitourinary, Head & Neck, Neurology, Sarcoma, Thoracic, other	8 (50)	62 (78)
Melanoma	4 (25)	0 (0)
Years in clinical practice - mean (95% CI)	13.8 (7.0 – 20.7)	10.9 (8.7 – 13.1)

The remaining overall study sample included both intervention and control clinicians and does not include clinicians caring for patients with melanoma since these patients and clinicians served as a pilot site.

TABLE 3. Examples of Transcript and Progress Note Documentation Including Rating of Concordance

Component of SICG and transcript	Documentation and location	Rating
Illness understanding *Clinician*: "What is your understanding of where you are with your illness? *Patient*: Excellent! We know right where we are. *Clinician*: And, and can you articulate for me what, you know, what that means? *Patient*: That means we understand, um, what the condition of my tumor is. We understand that there are several different, um, methods of treating it."	**Progress note** "He understands that he has an incurable tumor. He is interested in knowing detailed information about prognosis and treatment options."	Partially concordant
Information Preferences *Clinician:* "Um, so in terms of your disease, how much information do you like to receive about it? Do you want to know EVERYTHING? You want to know just, the…the bare minimum? It really differs between patients and we like to get a good sense. *Patient*: "Um... I like to know as much as I can…"	**Template** Information Preferences: Patient wants to be fully informed	Concordant
Prognostic Communication *Clinician:* "So, with regards to prognosis here, it's very difficult to actually peg what that is now. You know, like we said you had aggressive cancer that, a year ago we started this drug and essentially it's been stable ever since. So what does that mean? I don't, I don't know the answer. *Patient:* All right. *Clinician:* You know, we like to come in and high five each other and act happy about it, but it's entirely possible that it could start growing again next time." *Patient:* Yeah. Sure, I understand that and I'm ready for whatever comes"	**Progress Note** "We discussed prognosis, however, I noted that it is somewhat unclear what that would be. If the patient continues to have stable disease, we do have some patients who received Ipilimumab out for several years. Alternatively, it is possible that his next scan could show progressive disease and therefore his life expectancy could be less than a year in that situation."	Concordant
Goals *Clinician:* "So I, again, don't anticipate anything soon. But, let's say things don't go in the right direction. What would you like to accomplish, what would be your goals? What do you want to accomplish between now and then? *Patient:* Spend as much time with my children… and make an impact on my grandchildren, which is what I'm doing. *Clinician:* Um hmm…um hmm *Patient:* Umm… And not stop traveling. *Clinician:* Okay, and keep on… *Patient:* Keeping on until you say, you know…"	**Template** "Be physically comfortable, Be independent, Provide support for family." *Free text in addition to dropdown answers:* To be as active with her grandchildren and make a difference in their lives, and travel. She currently studies with her grandchild 3 x weekly	Concordant

TABLE 3. Continued

Component of SICG and transcript	Documentation and location	Rating
Fears/Worries *Clinician:* "And, and with THAT, what are your biggest fears? *Patient:* Um…well, my biggest fear is, is dying. You know, basically, you know, leaving my kids and my wife behind. *Clinician:* Um hmm…okay. *Patient:* That's, that's my biggest fear, to be honest with you."	**Template** Pain, Loss of control, Loss of dignity, Finances, Burdening others	Not concordant *(dropdown choices were selected that were not mentioned in conversation)*
Function *Clinician:* "What abilities are so critical to your life that you can't imagine living without them? And is, is communication one of those? *Patient:* Well...communication, um, the ability to be mobile... hearing... my sight. *Clinician:* So, does that mean if you were in a wheelchair, for example, like you... *Patient:* Yeah, well I could survive it, you know. It's not what I'd want, but I could survive it."	**Template** Being unable to talk, Being unable to interact with others. In addition to his ability communicate, he feels that his mobility and his vision are critically important.	Concordant
Tradeoffs *Clinician:* "Um if you become sicker, how much are you willing to go through for the possibility of gaining more time? Um for example: being on a machine, temporarily versus permanently, being in the hospital or intensive care unit, or having and feeding tube, that's just some of the… *Patient:* No, I wouldn't want to do that. *Clinician:* Okay. *Patient:* I wouldn't want to be in a position where I… where I wouldn't be able to function or walk around or, uh…but I would want to… *Clinician:* Okay." *Patient:* "Explore options such as surgery, radiation, things that, um…where I can still, uh…" *Clinician:* "Uh huh…okay." *Patient:* "Function after."	**Template** Patient does not want to: Be on a ventilator, Be in the ICU	Partially concordant
Family *Clinician*: "What are your kids' understanding of the disease? *Patient*: Well… they're really young. My older one knows. He knows that I got it and that someday I'm gonna… if I'm lucky I won't die of it but who knows. *Clinician*: Uh hm. *Patient*: But, my little ones, they know daddy's sick. So I've kind of tried to… say a little at a time."	**Progress note** "His wife is aware of wishes. He has a living will and a healthy care proxy. His younger children have a basic understanding that their dad is sick."	Concordant

Adherence (fidelity) to the conversation guide

Overall, clinicians addressed 87% of the 8 conversation guide components. The most commonly addressed were illness understanding and information preferences, which were discussed in all conversations. Preferences for family involvement in decision-making were discussed in all but one conversation. All other components, with the exception of prognosis, were discussed in 80-100% of conversations.

Thirteen percent of conversation components were not discussed. Sixty percent (15/25 conversations) of the conversations did not address prognosis. When asked about information preferences, 5 of the 25 patients did not want to know their prognosis and 2 said they only wanted the information their clinician deemed necessary. For the remaining 18 who wanted all information, prognosis was discussed with 10 of them (55% of the time). Rates of non-discussion of other conversation elements varied between 0 – 20% (illness understanding and goals, respectively).

Overall concordance

Figure 1 graphically displays the overall level of concordance of documentation in relation to audio-recorded conversation content. Overall, 43% of the information in all ACP conversations was fully concordant as documented in either a progress note or the template, ten percent of all information was partially concordant and eleven percent was not concordant. The remaining information (36%) was not documented.

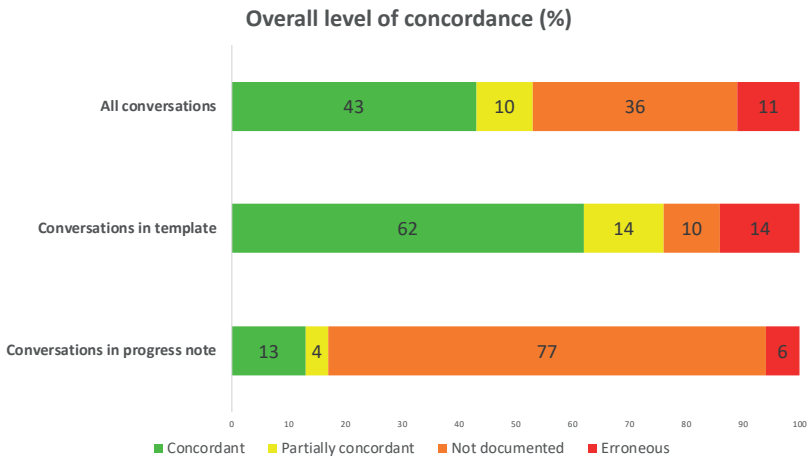

FIGURE 1: Graphical display of overall level of concordance for all conversations, conversations documented in the template and conversations documented in the progress note. Rounded percentages are displayed instead of absolute values.

Figure 2 provides a graphical display of each element of the SICG and the concordance rating. For clarity, concordance ratings for all conversations, conversations documented in the template (N=16), and conversations documented in the progress note (N=7) are displayed separately. Overall, components for which we observed the highest rates of concordance centered around family (15/24 conversations in which family was discussed; 60%) and goals (12/20 conversations; also 60%). We observed the highest partial concordance rate in relation to illness understanding (7/25 conversations; 28%) and information preferences (4/25 conversations; 16%). The highest rate of not concordant (erroneous) documentation was found for prognostic communication (3/10 conversations; 30%) and illness understanding (4/25 conversations, 16%).

FIGURE 2: Graphical display of conversation-documentation concordance for each of the elements of the Serious Illness Conversation Guide. Absolute values, instead of percentages, are displayed for clarity.

Not concordant or erroneous documentation

Of the information rated as not concordant (11%) in all available documentation, we identified two conversations in which inaccurate documentation could potentially lead to patient harm. Both of these examples were in template notes, and involved dropdown menus. In both of these instances, information not articulated during the conversation by the patient was included in the template documentation. First, based on the audio-recording, a patient had described his goals as: "*To live as long as possible, as long as I am comfortable*." The clinician documentation, as selected from dropdown options, reflected the patient's goals as: "*To be physically comfortable, not to be a burden, be independent."*

Second, one patient described that he would be "*Willing to fight"* as long as he was not in pain. The clinician documented, again from the dropdown, that the patient "*Does not want to undergo aggressive tests and/or procedures."* In both of these cases, the documentation diverged significantly from what the patient had expressed, and could lead to a limitation on life-sustaining treatment not aligned with the patient's expressed wishes. We did not observe similar inaccuracies in the documentation using the free-text progress notes or any other instances in which erroneous information was included in the documentation.

Not documented

Of the conversational information rated as not documented (32%), conversation elements most frequently discussed but not documented primarily pertained to function (11/24 conversations; 46%), fears/worries, and tradeoffs (both 10/23 conversations, 43%).

Documentation in the template versus progress note

Overall, documentation in the progress note alone (N=7) accorded with conversation content less frequently (13%) compared to documentation in the template (62%). Using the template, documentation regarding family was most commonly fully concordant (13/16 conversations; 81%) followed by documentation regarding information preferences and goals (each fully concordant in 11/16 conversations; 69%). In contrast, documentation about illness understanding was fully concordant in only 5/16 conversations (31%). Documentation about goals, tradeoffs and prognostic communication was most frequently rated as erroneous (not concordant). Clinician documentation when using a progress note was concordant much less frequently. In fact, documentation of elicited information was absent for a majority (64%) of key elements discussed.

DISCUSSION

The use of an evidence-based guide and the associated training program led to a high level (87%) of adherence to the key elements of an advance care planning conversation in the setting of serious illness. However, only 55% of these conversations addressed prognosis among patients who explicitly expressed a desire for this information. In addition, this study represents the first reported evaluation of EHR documentation concordance with information elicited in audio-recorded ACP conversations. We observed full concordance of conversations and documentation in approximately 43 percent of our sample. Significant, clinically-meaningful information elicited by clinicians in these conversations was often not fully documented in the EHR, most commonly with regards to illness understanding, fears/worries, and tradeoffs. These findings demonstrate that the use of the SICG supports clinicians in eliciting a high proportion of critical information from patients; however, in spite of a streamlined system for recording information in the EHR, less than half of this important information was recorded anywhere in the EHR.

Even when clinicians did document in the EHR, only two thirds of the conversation documentation was readily retrievable in the template, and thus available during a potential medical crisis. In spite of a multi-component intervention that included a set of structured questions to guide conversations, a clinician training program that emphasized the importance addressing all the elements of the SICG, the value of documenting conversations in the EHR, and provided a documentation template to structure and streamline the documentation process,[9] many discordances between conversations and documentation were found. Further understanding of why the strategies used in this intervention were only partly effective, and of other possible barriers to clinician understanding of patients' responses and their documentation is needed. If confirmed by larger studies, our findings add to serious concerns raised in multiple other studies about documenting ACP conversations and about the ACP process more broadly.[11–14]

Is it essential that each of these conversation elements be discussed and documented, especially when the extent to which each of these elements contribute to patient outcomes is unknown? Clearly, more research is needed to answer this question. However, all components included in the SICG were developed and tested with input from patients and endorsed by the High Value Task Force of the American College of Physicians.[3] Although some might question the importance of documenting all components of an ACP conversation, documenting a patient's (mis)understanding of prognosis or expected illness trajectory may lead clinicians to further explore these issues and implement changes in their care plan. For example, the information

provided may not have been clear, the patient may be confused due to cognitive or language barriers, or the patient may actively be working to avoid an undesirable reality.[15,16] Clearly, more research is needed to further answer these questions.

Our findings did highlight two potential gaps that are likely to contribute to poor documentation: not addressing key elements of a high-quality, serious illness conversation (e.g. prognostic disclosure), and not documenting key information elicited during the conversation. Overall, clinicians demonstrated a high degree of fidelity to the guide, with the majority including seven of the eight possible conversation elements in their serious illness conversations. However, in spite of the structure of the SICG and our training program that emphasized prognostic disclosure as desired by the patient, by far the most frequently omitted element was prognostic discussion. Clinician discomfort with prognostic discussions is likely to lead to avoidance of a prognostic discussion.[17–19] Although no data are currently available to show that prognostic disclosure improves outcomes, studies have shown that understanding the possibility of a limited prognosis is associated with patient preferences for less aggressive care.[20,21] This suggests that enhanced training of clinicians to sensitively address prognosis in patients could result in clinician behavior changes that promote more patient-centered care.

Further, time pressures, documentation requirements, and negative attitudes regarding the EHR are widely recognized and likely contribute to poor documentation by clinicians.[13,14] Since many other routine, and important informational elements (e.g. documentation of allergies) are documented much more consistently and accurately, one might ask whether incomplete documentation of end-of-life preferences could be a reflection of aspects within the culture of medicine that devalue the importance of such planning and information sharing.[22]

We were able to identify one approach that holds potential for improving concordance of documentation and ACP conversations: the use of a template was associated with a higher rate of concordance than documentation in a progress note. Because a template has discrete fields for each question and answer, it might serve as a trigger for a clinician's memory about the specifics of a conversation or make the documentation demands easier. Indeed, such templates have proven useful when it comes to improving documentation in other areas of medicine, for example in the documentation of obesity in primary care clinics.[23] A potential drawback in the use of dropdowns might be that the impreciseness of pre-specified dropdowns make lead clinicians to include erroneous information, which could pose a danger to patients. Reassuringly, we only observed two instances in which a clinician included erroneous information in the template.

Yet, it is also important to recognize that we observed limited template responses to several questions (e.g. illness understanding or tradeoffs). It may be that responses to such open-ended

question are not easily encapsulated in a predefined dropdown menu and supplementing additional information using a free-text field may be part of the solution. In particular, the question regarding how much a patient is willing to go through for the sake of more time has the potential to inform decision-making about how the patient sees the risks and benefits of future care options. This often-subtle and nuanced information about patient values, goals, and preferences can be critical to patient-centered decision-making. While inaccurate documentation represents one potential hazard, absent or incomplete documentation, which we observed more frequently than erroneous documentation, represent potential safety concerns as well, and could contribute to provision of goal-discordant care.

We note multiple limitations in this study. This is a very small sample drawn from a single institution. Both patients and clinicians declined to participate in this part of the study at high rates. The sample thus represented a small subset of overall study participants, and was prone to self-selection bias among both patients and clinicians , as patients who participated may have been less anxious about this conversation, and clinicians who agreed to have their conversations audio-recorded might represent good communicators with the best documentation practices. Our comparison of template and free-text notes is very small, yet provides hypotheses for future study. Our analysis also has potential for analytical bias, with possible documentation misclassification. Yet, we worked to address this through the use of independent ratings and verification through a third, independent researcher when necessary. Larger studies, using carefully designed and well-validated measures of conversation and documentation quality, are clearly needed. Finally, although the number of conversations elements not discussed are briefly described in this analysis, it is worth noting that this study is not aimed to offer a rigorous analysis of fidelity to the intervention but instead aimed to describe practices surrounding documentation.

Overall, our study offers positive findings about clinician fidelity to our conversation guide, while also suggesting that there are significant opportunities to improve the quality of ACP conversations and the concordance between conversations and documentation, even in a context in which tools, training and systems support are in place. Further research is needed to better understand how to overcome clinician failure to initiate prognostic discussion, and to enhance documentation about specific key areas such as illness understanding, tradeoffs, and fears/worries that provide key information for subsequent clinical decision-making. Finally, and importantly, research is needed to evaluate whether improved conversations and documentation result in better care for seriously ill patients.

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SUPPLEMENTS

SUPPLEMENTARY TABLE A. Serious Illness Conversation Guide and dropdowns in the Electronic Health Record Template

Element	Serious Illness Conversation Guide	Dropdown options in EHR template
Illness understanding	What is your understanding now of where you are with your illness?	• No understanding of prognosis • Overestimates prognosis • Appropriate understanding of prognosis • Underestimates prognosis
Information preferences	How much information about what is likely to be ahead with your illness would you like from me?	• Patient wants to be fully informed • Patient wants to be informed of big picture, but not details • Patient wants some information, but no "bad news" • Patient does not want any information for him/herself
Prognostic communication	Share prognosis, tailored to information preferences	• More than a year • Several months to year • Several weeks to month • Days to weeks • Did not discuss and why ____
Goals	If your health situation worsens, what are your most important goals?	• Live as long as possible, no matter what • Be at home • Be physically comfortable • Be mentally aware • Not be a burden • Be independent • Have my medical decisions respected • Provide support for my family • Be spiritually and emotionally at peace • Achieve particular life goal, please specify
Fears/Worries	What are your biggest fears and worries about the future with your health?	• Pain • Emotional distress • Concerns about meaning of life • Ability to care for others: children, ill spouse • Loss of control • Loss of dignity • Finances • Other symptoms • Spiritual distress • Burdening others • Other family concerns • Getting treatments I do not want • Preparing for death • Other

SUPPLEMENTARY TABLE A. Continued

Element	Serious Illness Conversation Guide	Dropdown options in EHR template
Function	What abilities are so critical to your life that you can't imagine living without them?	**Unacceptable Function:** • Being unconscious • Being unable to talk • Being in pain or very uncomfortable • Not being myself • Not being able to care for myself, including toileting and feeding • Being unable to interact with others
Tradeoffs	If you become sicker, how much are you willing to go through for the possibility of gaining more time?	**Patient does not want to:** • Be on a ventilator • Live in a nursing home • Be uncomfortable • Be in the hospital • Be in the ICU • Undergo aggressive tests and/or procedures • Have a feeding tube
Family	How much does your family know about your priorities and wishes?	• Extensive discussion with family about goals and wishes • Some discussion, but incomplete • No discussion but plans to address these issues • No discussion; wants help in talking to family • Wants clinician to talk with family • Does not want family informed

VII

Chapter 7

Cancer survivorship and palliative care: Shared progress, challenges and opportunities

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INTRODUCTION

The number of cancer survivors is growing rapidly and it is anticipated that a large proportion of the expected 20 million individuals will be older than 65 years of age in the coming decade.[1] This "rising tide" of cancer survivors requires more complex care due to increased comorbidity.[2] As such, effective strategies addressing the heterogeneous needs of this growing population, while making efficient use of our healthcare system, are vitally important.[3]

Although much progress has been made, particularly over the past decade, there are remaining gaps in the care that cancer survivors receive and questions regarding how to meet the workforce demands and provide optimal care for this expanding population.[4,5] In the U.S. and abroad, various models are in place that aim to effectively integrate care for cancer survivors into routine clinical care.[6,7] However, these are highly individualized per setting, are not systematically delivered or evaluated for outcomes,[6] and there is thus no consensus on what, and whether, an optimal model exists or can be developed.

In parallel to growing attention on caring for cancer survivors, an increased focus on integrating palliative care for cancer patients over the past two decades has highlighted potential benefits.[8–10] However, the field faces significant challenges. As with survivorship care, there is no consensus on the best approach to integrate palliative care into routine practice and readily available, cost-effective, models have not been widely disseminated into clinical settings.[11–13] Likewise, the increased workforce demands necessitate new delivery models across settings with diverse resources and levels of palliative care expertise.[11,14,15]

In this commentary, we aim to describe the progress and challenges for both survivorship and palliative care for patients with cancer and offer insights into opportunities to advance the quality of health care delivery in both fields.

Definitions

The terms "survivorship care" and "palliative care" are both associated with uncertainty about who provides the care and what it entails. Survivorship care, while applicable to those living with or beyond cancer, is often restricted in definition to the phase of care following completion of active treatment.[16,17] Nevertheless, the National Cancer Institute defines a cancer survivor as an individual "from the time of diagnosis, through the balance of his or her life", and includes "family members, friends and caregivers who are impacted by the survivorship experience."[18] Varying use and interpretations of the definitions confuse patients and clinicians alike about what survivorship care truly means.[19] Further, terminology may be problematic as not all

patients want to take on the label of "cancer survivor" and its associated advocacy role.[20,21] Although a survivor is defined from diagnosis forward, in this commentary, we define the period covered by "survivorship care" as the period following primary cancer treatment.

Similarly, palliative care is often confused with end-of-life or terminal care by patients and clinicians, whereas caring for patients very near to the end of life is a small portion of comprehensive palliative care.[12] We define palliative care as care focused on providing patients relief from the symptoms and stress of a serious illness with the goal of improving quality of life for both the patient and the family.[22] To differentiate this area from "survivorship", we focus on those living with advanced, chronic or terminal cancer. The American Society of Clinical Oncology guideline recommends that palliative care begin early in patients' treatment[23] due to clear evidence that palliative care concurrent with traditional oncology treatment offers significant benefits, including extending life itself.[8,9,24] However, access to quality palliative care for all patients suffering from advanced cancer remains low and caregivers often feel that it is provided too late.[25,26]

Palliative and survivorship care should acknowledge the confusion, debate and uncertainty in the terminology used in both fields. Clarification and further specification of the phase of care being described or offered is needed in educational, clinical, research and policy discussions. Clinicians must also recognize that patients may have different understanding, preferences and expectations of what palliative and survivorship care are and what they can offer. Both fields may consider how narrowing or broadening their definition may impact their acceptability and reach.

Patient-centered care

A defining and important aspect of both survivorship and palliative care is the impetus to shift from disease-centered to patient-centered care. The Institute of Medicine report entitled "*Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis"* addressed cancer care across the continuum and emphasized patient-centered care that is "respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions."[27]

Survivorship care and palliative care both aim to provide patient-centered, supportive care focused on enhancing function, improving the quality of life (QoL) of both patients and caregivers, addressing distress and persistent symptoms such as pain, and encouraging shared-decision making between clinicians and patients. The alignment of patients' personal values to guide clinical decisions is relevant and inherently actualized in palliative care through shared decision making. Engaging patients in decision making may be less emphasized in survivorship care but is still of vital importance since evidence for many interventions, for example,

surveillance imaging for recurrences or late effects, is still lacking but often recommended. Factors that may have a significant role in patient-centered care are the duration and intensity of the relationship between the patient and the provider. It is worth noting that both palliative and survivorship care may be longitudinal (typically spanning months to years), survivorship care visits typically occur less frequently as the duration of time since therapy lengthens. Moreover, discussions may focus on restoring or retaining function, and are usually oriented towards achieving long-term goals whereas palliative care visits occur more regularly, discussions may focus on symptoms control and may be oriented toward short-term goals. As an example, while accepted for management of pain in palliative care, long-term management with opioids in cancer survivors is ridden with potential concerns[28] and, even if potentially patient-centered, not desirable.[29,30]

Clearly, there are also important financial as well as insurance-related barriers that must be overcome in both fields. Cancer survivors face significant financial sequalae after diagnosis and, in the United States, cancer-related financial burden has been well documented.[31,32] In palliative care, insurance coverage and access to hospice services are not universally available, leading to disparities in care quality and delivery.[33] Ensuring that all patients are adequately covered and that healthcare providers are reimbursed for providing survivorship and palliative care services is of critical importance.

Palliative and survivorship care need to continue efforts toward the provision of patient-centered care that takes into account patient preferences and promotes shared decision making. Achieving this goal will require a multi-modal approach that includes provider and patient education, health care delivery, payers and research.

Workforce and training

A large gap between supply and demand in oncology care has been predicted in the coming years in the U.S. and abroad and likely affects the expected gaps in workforce for both palliative and survivorship care.[15,34,35] A further complication in this era of demand is the lack of adequate attention to both fields in a majority of clinical curricula.[36,37] However, in both the U.S. and Europe, palliative care has gained increased official recognition as a subspecialty, indicating that a unique set of skills and knowledge and advanced clinical training are required to practice specialty-level palliative care.[38,39] In contrast, survivorship care clinicians have no required training and the field has not been recognized as a subspecialty.

Several strategies have been promulgated to combat this gap between supply and demand. These include an increase in the number of working clinicians, further training of advanced practice providers such as nurse practitioners or physicians assistants, and expanding the role of healthcare providers without specialty oncology or palliative care training.[27] Still, both palliative

and survivorship care will likely require a multifaceted strategy to grow and prepare the current workforce to meet the increasing demand.[34] Building bridges between disciplines (including primary care) and leveraging the value and expertise of different healthcare professionals is of critical importance to grow and sustain a workforce that is capable of providing quality palliative and survivorship care in the coming years. An increased focus on medical, nursing, and allied health curricula while incorporating training and continuing medical education programs is also essential.

Health care delivery

Oncology providers often feel that they are most suited to continue caring for survivors, and report concerns about primary care-based care for cancer survivors.[40–42] Patients expect follow-up visits with oncologists, primarily to detect recurrences, and value consistency and continuity of care.[40,43] Moreover, patients often do not want to give up the relationship with a provider after sharing such an intense experience and express uncertainty regarding the skills and knowledge of primary care providers about their cancer survivorship needs.[42,43] The increasing number of cancer survivors and shortage of oncology providers also requires a shift from oncology-based care to models that incorporate other disciplines and professions.[34,44,45] For example, a risk-stratified approach to identify cancer survivors most in need of direct interventions may be a useful model to provide care based on risk of long-term or late effects and individual needs.[46] This approach could mean that "onco-generalists" (internists with expertise in cancer care) can serve as cancer survivorship experts in addition to engaging both primary care providers and oncologists in providing optimal care for cancer survivors.[45]

While early integration of palliative care is now advocated for as the standard of oncology care, healthcare providers still struggle to identify the most optimal model for delivering such care. Whereas palliative care initially provided services via hospice and hospital-based consultation models, the impetus to provide broader and earlier care to more patients is pressuring the expansion of palliative service capabilities. In the U.S., the field has been strategically shifting into the outpatient settings for over a decade.[47] Evidence suggests that efforts to expand delivery of services to the outpatient and home-based palliative care models benefits both patients and families.[48,49] Further expansion of reach via home-based programs and telemedicine also represent ongoing evolutions of the palliative care model. Similar to survivorship efforts to engage other hybrid providers such as onco-generalists, palliative care is putting significant focus on promoting expertise for advanced practice providers who specialize in oncology to deliver primary palliative care.[22]

Importantly, while models address the location of care and reach more patients, there needs to be greater clarity on which services are most helpful across different settings and providers.[11,49,50]

Although more work is needed, a number of measures evaluating end-of-life quality markers are readily available and have been endorsed by consensus-based entities such as the National Quality Forum.[51–53] In contrast, quality survivorship care metrics are mostly lacking[4,54] and the field may draw examples from palliative care through comparable studies using similar, rigorous methodologies. Having such quality markers available is important when moving healthcare towards new, cost-effective models of value based repayment and would also enhance the consistency of care delivery and permit comparison of different models of care across settings. Last, there is a clear need for computer-based clinical decision support to further enhance the quality of care delivery in both fields. Routine integration of easy to use, evidence-based tools within the electronic health record systems is urgently needed.[55]

Research

The quality of research in survivorship care has improved in recent years but there are still key gaps that need to be addressed.[56] The Children's Oncology group has led the field in developing guidelines that have been established through high-quality research in the pediatric population.[57,58] Over the past decade, survivorship-based guidelines have been developed for adult cancers, though evidence for many of the recommendations is still lacking.[4,54] Most research to date has focused on breast cancer whereas research lags in cancers with similar survival rates.[56] There is also lack of interventional studies, those involving younger and long-term cancer survivors.[58–61] Further, most studies tend to measure outcomes related to well-being and QoL.[59,61,62] Although such outcomes are of importance, there is a paucity of studies examining key biologic or genetic components of long-term and late effects of cancer.[56] A multi-faceted understanding of the drivers of chronic and late effects is needed to both identify at-risk patients for intensive follow-up and to tailor specific interventions to address such issues. Another shortcoming is the availability of metrics to measure the quality of survivorship care.[4,63,64] Measures such as QoL or well-being may not be sensitive or responsive enough to detect quality differences in survivorship care interventions.[63,65]

On the contrary, palliative care research has been growing and many of the most recent clinically influential studies in the field have been centered around oncological diseases.[66] Although well developed in survivorship care, pediatric palliative care is still very much a growing field and opportunities to further emphasize research in this field remain.[67–69] International studies have shown various benefits of earlier integration palliative care in terms of QoL, healthcare utilization, levels of patient and caregiver distress, and even survival.[9,24,70,71] As a result, models to introduce earlier palliative care concurrent with standard oncology treatment have received increased recognition. Yet, dissemination of cost-effective and reproducible models remains an important challenge, thus large-scale, randomized trials using predefined quality metrics to demonstrate sustained benefit are needed. Use of novel technologies such as telehealth,

as well as dissemination and implementation methodologies would facilitate the scaling of existing proven models and expand testing their effect on different outcomes.[11,72,73] To work on such research priorities, both fields need to overcome the institutional and funding barriers currently in place.[56,74,75] The Cancer Moonshot initiative to further accelerate cancer research is a much-needed step in the right direction.[76]

Opportunities for shared and actionable next steps

Palliative and survivorship care have made important strides, and despite seeming superficially paradoxical, the two fields may have more in common than in opposition. An increased focus on collaboration and a pursuit of shared strategies may foster significant advances in both fields and help patients with and beyond cancer receive high-quality patient-centered care. Figure 1 provides an overview of the similarities and differences between the two fields as well as opportunities for shared and actionable next steps.

In order to achieve these steps, we propose the following: first, both fields need to acknowledge and clarify the existing confusion on terminology through marketing campaigns and education targeted at patients as well as providers. Second, palliative care and survivorship care need to continue collaboratively leading the movement towards the provision of patient-centered care through education and training of providers, engagement of patients and their caregivers, as well as development of systems that incorporate decision tools into direct patient care. Third, expansion and enhancement of a multi-disciplinary workforce is of critical importance, and may be achieved through education, training and involving a broader community of health care providers who may collaboratively care for patients across the continuum of survivorship and palliative care. Fourth, cost-effective models of care delivery need to be identified, tested and implemented. Models should make use of emerging, innovative technologies to deliver care at the point-of-need to patients across different clinical settings. Lastly, there is a clear need for quality metrics to measure the efficacy of these models. Such metrics will allow for consistency of measurement and should be able to both evaluate and identify the quality of care.

Palliative and survivorship care are distinct but yet have shared successes, remaining challenges and opportunities. We hope that an increased focus on collaboration may foster significant advances to both fields and help patients with and beyond cancer receive high-quality, patient-centered care.

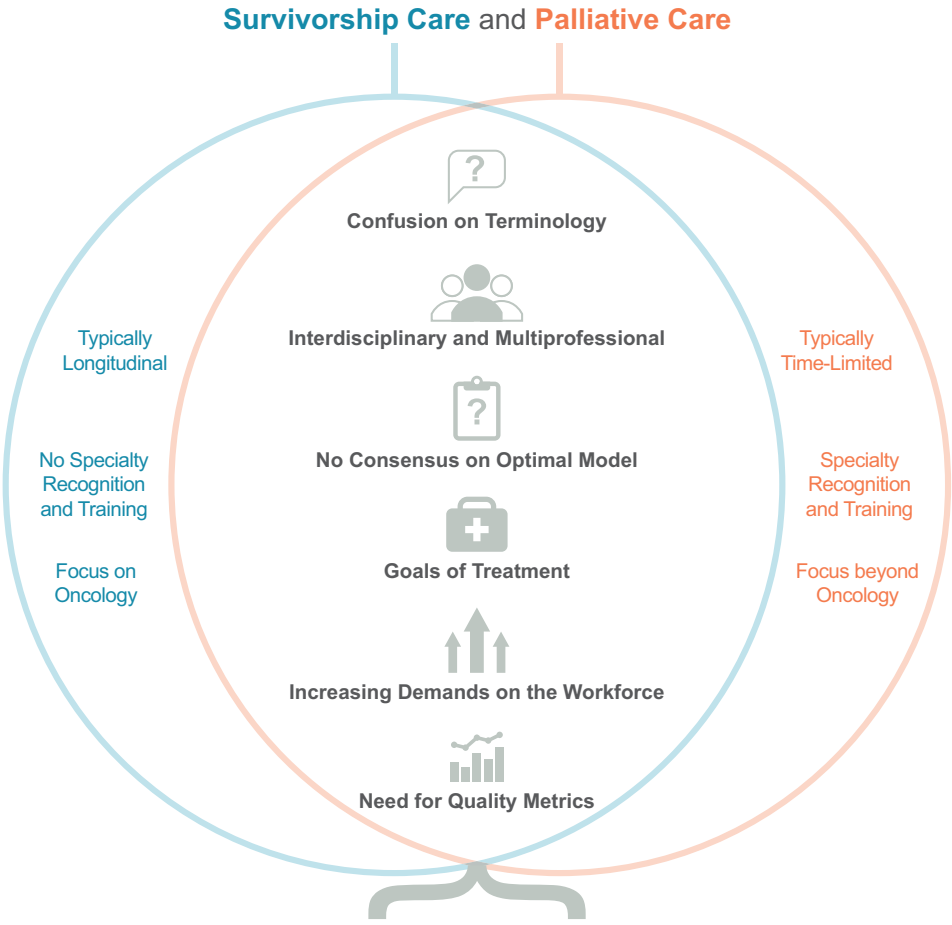

FIGURE 1. Venn diagram illustrating shared opportunities for collaborative learning and actionable next steps for the fields of survivorship care and palliative care.

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VIII

Chapter 8

Health-related problems in adult cancer survivors: Development and validation of the Cancer Survivor Core Set

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ABSTRACT

Purpose: Improved survival rates from cancer have increased the need to understand the health-related problems of cancer treatment. We aimed to develop and validate a 'Cancer Survivor Core Set' representing the most relevant health-related problems in adult cancer survivors using the International Classification of Functioning, Disability, and Health (ICF).

Methods: First, a Delphi study was conducted to select ICF categories representing the most relevant health-related problems. Three Dutch expert panels, one each for lung, colorectal, and breast cancer. Each panel comprised lay experts and professionals. The experts reached within- and between-panel consensus in two rounds (≥70% agreement). Second, a validation study was performed. Generic cancer survivorship questionnaires assessing health-related problems or quality of life among cancer survivors were selected. Items of selected questionnaires were linked to the best-fitting ICF category and to the selected ICF categories from the Delphi study, respectively.

Results: In total, 101 experts were included, of which 76 participated in both rounds, reaching consensus on 18 ICF categories. The Distress Thermometer and Problem List, the Impact of Cancer (v2), and the Quality of Life in Adult Cancer Survivors questionnaires were selected for the validation study, which led to the inclusion of one additional ICF category.

Conclusions: The developed Cancer Survivor Core Set consisted of 19 ICF categories representing the most relevant health-related problems in adult cancer survivors: five from the 'Body Functions and Structures' component, eight from the 'Activities and Participation' component, and six from the Environmental Factors' component.

INTRODUCTION

Earlier detection of malignant conditions, improved diagnostics, and new treatment modalities, mean that the number of adult cancer survivors has increased substantially in most Western countries and is estimated to rise further in the near future.[1–3] Thus, the long-term effects of a cancer diagnosis are important to both research and clinical practice. Primary health-related problems include those related to the malignancy itself, surgical treatment, and the toxicity of adjuvant therapy.[4,5] Moreover, psychosocial symptoms are reported, such as fear of recurrence, disturbance of self-image, anxiety, depression, difficulties with return to work, and financial concerns.[6–8]

It is important to understand and address the problems affecting adult cancer survivors.[5,9] Therefore, screening instruments have been developed for specific health-related domains (e.g. health worries or body image concerns[10]) or subgroups of cancer survivors (e.g. prostate cancer survivors).[11] One such tool, the World Health Organization International Classification of Functioning, Disability, and Health (ICF), is a globally accepted classification that broadly represents human functioning, in a unified language. However, the ICF is cumbersome for use in daily practice, and derivatives have been developed for specific patient populations. These 'core sets' list the ICF categories for specific conditions (e.g., breast cancer[12]) or settings (e.g., rehabilitation).[13] To date, no core set has been established for the health-related problems of adult cancer survivors in general. Thus, we aimed to develop and validate the Cancer Survivor Core Set covering the most relevant health-related problems faced by cancer survivors.

METHODS

Study design

To develop the Cancer Survivor Core Set, we performed a Delphi study[14] followed by a validation study.[15] In the Delphi study, we aimed to achieve consensus on the most relevant ICF categories for cancer survivors,[16,17] while prioritizing the patients' perspective. In the validation study, we then assessed the content validity of the ICF categories using a linking procedure.

Delphi study

Composition of the expert panels

We defined adult cancer survivors as adults aged 18 years and over who had survived more than one year after diagnosis.[18] Panels were formed for lung, colorectal, and breast cancer. These cancers were selected based on current and projected rates of survivors adversely affected by health-related problems;[19] indeed, large increases in the numbers of survivors are anticipated.[20]

There was a minimum of 25 survivorship experts per panel, with balanced proportions for three subpanels: experts by experience (lay experts), medical experts, and other healthcare workers (nine subpanels in total). We aimed to include lay experts who were able to reflect on the relevance of the ICF-categories in adult cancer survivors based on more than their personal disease experience (a transcending view). Lay experts were selected through consultation with and advice from patient associations in the Netherlands.

Medical experts and other healthcare workers were selected through healthcare (or healthcare affiliated) organizations. Medical experts could be physicians or nurse practitioners. A physician could either be a medical oncologist, surgical oncologist, plastic surgeon, radiation oncologist or radiologist. All healthcare workers had to be directly involved in the treatment of oncology patients or survivors. We invited potential experts to participate in the study by telephone or e-mail, and provided written information. When lay experts judged themselves as being unable to have a transcending view they were excluded from participation. Experts who provided informed consent were included in the Delphi study. According to our institutional review board, no approval was needed because this was a non-invasive study and not subject to the Dutch Medical Research Involving Human Subjects Act.

ICF categories

All ICF categories were divided into three components: 'Body Functions and Structures' 'Activities and Participation' and 'Environmental Factors'. The Body Functions and Structures component covers functioning at the body level, while the Activities and Participation

component covers an individual's functioning. Environmental Factors are factors possibly influencing functioning as either facilitators or barriers.[21] Each ICF component is further subdivided into three levels for more detail.

Delphi procedure

All 265 second-level ICF categories were used for item selection to avoid selection bias. ICF categories related to the Body Functions and Structures component were only sent to the expert medical subpanels, because adequate evaluation required specific medical knowledge. Based on guidelines[17] and similar studies,[22,23] the Delphi study consisted of at least two rounds in order to achieve consensus.

During the first round, experts received the ICF categories with the corresponding description for coding, definition, inclusion, and exclusion. Experts were asked to evaluate the relevance of each ICF category (expressed by severity and/or frequency of a problem) for their cancer type. Response options were: 'not relevant' (score 1), 'hardly relevant' (score 2), 'somewhat relevant' (score 3), 'relevant' (score 4), 'very relevant' (score 5), and 'I cannot judge this ICF category' (score 0). Items selected in the first-round analysis were presented to each panel in a second round, when experts were asked to evaluate whether they agreed with inclusion or exclusion of ICF categories (see data analysis). Experts did not meet face-to-face and they completed their assessments independently, either online or on paper. Participation could be refused at any point, and non-responders received two reminders.

Data analysis

Data analysis was performed using IBM SPSS Version 20.0 (IBM Corp., Armonk, NY, USA). The median scores, response frequencies, and percentages of panel responses were calculated per ICF category. Several analyses were performed after the first round to determine which ICF categories to include in the second round:

1. Median scores per subpanel (lay experts, medical experts, other healthcare workers) were calculated for each ICF category.
2. Median scores per panel (lung, colorectal, breast) were calculated for each ICF category. When the lay expert subpanel rated an ICF category as more relevant than the overall panel, the median score was adjusted to that of the lay expert subpanel.
3. An ICF category was included in the second Delphi round as a 'very relevant' category if the median score of at least one of the three cancer panels was scored 5 and the score in the other two panels was ≥3.
4. An ICF category was included in the second Delphi round as a 'relevant' category if the median score of at least one of the three cancer panels scored 4, the other panels evaluated the ICF category with a score ≥3, and no panel gave a score of 1.

After the second round, the content validity index (CVI) was assessed for each ICF category. This index is the proportion of respondents agreeing with the proposed relevance of the ICF categories.[24] If the subpanel of lay experts scored a higher CVI compared to others in their panel, the percentage was adjusted to the highest percentage. ICF categories scoring a CVI ≥0.70 in all cancer panels were included in the initial Cancer Survivor Core Set.

Validation study

Questionnaire selection

To detect cancer survivorship questionnaires that are widely used and sufficiently validated, a semi-structured literature review was performed in a single database using a limited number of search terms and strings. Eligible questionnaires were retrieved from the PubMed database (2000–2015) using MeSH-terms in the search strings including: (("Survivors"[MeSH]) AND "Neoplasms"[MeSH]) AND "Surveys and Questionnaires"[MeSH]. We selected questionnaires that were developed by patient involvement at some stage. In addition, questionnaires were required to be 1) generic for cancer survivors, 2) assessing health-related problems or quality of life, 3) available online and in English, 4) have sufficient psychometric properties, illustrated by at least two validation studies, and 5) have demonstrated sufficient clinical utility in at least one study describing the use of the questionnaire in a cohort of cancer survivors. All eligible questionnaires were screened using these inclusion criteria.

Linking procedure

Two researchers with experience in oncology and working with the ICF (OG and KW) independently performed the linking procedure, according to the updated ICF linking rules.[25] Both researchers linked the items of the selected questionnaires to the most closely matching ICF category. Any discrepancies were discussed until consensus was reached, and a third independent researcher (AJB) was consulted if disagreements could not be resolved.

Items within questionnaires measuring positive changes after diagnosis (e.g. *Having had cancer has made me more willing to help others*) were excluded from the linking procedure, because the aim was to select health-related problems. The remaining questionnaire items could either be linked to an ICF category in the initial Core Set, be linked to an ICF category not in the initial Core Set (e.g. a newly identified ICF category), or not be linkable to any ICF category. It was possible to link more than one item to the same ICF category. If a new ICF category was identified on all questionnaires, it was added to the final version of the Cancer Survivor Core Set.

RESULTS

Delphi procedure

Expert panels

In total, 441 potential experts were contacted, 101 of whom confirmed their expertise. Experts were evenly distributed across the panels and subpanels (Table 1). All experts completed the first round, and 76 experts (75%) completed the second round assessment.

TABLE 1. Number and characteristics of experts across panels during the first (I) and second (II) Delphi round[a]

	Lung cancer		**Colorectal cancer**		**Breast cancer**		**Total expert panel**	
	I	**II**	**I**	**II**	**I**	**II**	**I**	**II**
Subpanel - Lay experts								
Lay expert	13	10	10	8	21	12	44	30
Subpanel – Medical experts								
Physician	3	2	9	5	5	5	17	12
Nurse practitioner	4	4	2	2	3	3	9	9
Subtotal	7	6	11	7	8	8	26	21
Subpanel - Other healthcare workers								
Oncology nurse	9	7	4	3	3	3	16	13
Psychologist	1	-	-	-	1	1	2	2
Dietician	1	1	1	1	-	-	2	2
Social worker	1	1	1	1	2	1	4	3
Physical therapist	-	-	1	1	6	5	7	5
Subtotal	12	9	7	6	12	10	31	25
Total	**32**	**25**	**28**	**21**	**41**	**30**	**101**	**76**

I = Delphi round one
II = Delphi round two
A dash indicates no expert participating in that subpanel or the overall panel
Adult cancer survivors were defined as adults living more than one year after their diagnosis, and who were eligible for participation; potential survivors were selected based on their ability to give an overview and their expertise on health-related problems

ICF category sampling

The results of the ICF category selection process throughout the Delphi procedure are detailed in Table 2. After the first Delphi round, 21 ICF categories were evaluated as 'very relevant' and 140 ICF categories were evaluated as 'relevant'. In the second Delphi round, all selected ICF categories from the Body Functions and Structures component were included, but two ICF categories from the Activities and Participation component (*d410 Changing basic body*

position; d530 Toileting) and one ICF category from the Environmental Factors component *(e420 Individual attitudes of friends*) were eliminated. Participants agreed not to include any of the 140 ICF categories categorized as 'relevant' in the second Delphi round. Due to the high level of consensus, there was no need for a third Delphi round. Thus, the initial Cancer Survivor Core Set comprised 18 ICF categories, of which 10 (56%) were added by the lay expert subpanels.

TABLE 2. Number of selected categories per ICF component after each Delphi round

	ICF component			
	Body Functions and Structures n (%)	**Activities and Participation n (%)**	**Environmental Factors n (%)**	**Total n (%)**
Number of initial categories in the ICF	119 (45)	82 (31)	64 (24)	265 (100)
Delphi round I selection				
Very relevant	4 (19)	10 (48)	7 (33)	21 (100)
Relevant	55 (39)	53 (38)	32 (23)	140 (100)
Delphi round II selection	4 (22)	8 (44)	6 (33)	18 (100)

Percentages may not add up to 100 due to rounding
ICF, International Classification of Functioning, Disability, and Health

Validation study

Selected questionnaires

In total, 15 questionnaires (Supplementary Table A) were retrieved, of which three met the inclusion criteria: the Quality of Life in Adult Cancer Survivors (QLACS),[10] the Dutch version of the Distress Thermometer and Problem List (DT/PL),[26,27] and the Impact of Cancer version 2 (IOCv2) (Table 3).[28] These three questionnaires each included 47 items. After exclusion of the positive items, we subjected 116 items to the linking procedure (39 items of the QLACS, 47 items of the DT/PL, and 30 items of the IoCv2).

Items linkable to the ICF categories in the initial Core Set

It was possible to link 70 items to ICF categories in the initial Core Set. We linked 32 items from the QLACS and 15 items from the DT/PL to 8 ICF categories, and 23 items from the IOCv2 to six ICF categories (Table 4).

Newly identified ICF categories

In total, 43 items were linked to 26 newly identified ICF categories: 6 items from the QLACS, 31 items from the DT/PL, and 6 items from the IOCv2. One new ICF category—*b130 Energy and drive functions*—was identified in each questionnaire and added to the initial Core Set. Another three ICF categories were identified in two questionnaires (*b126 Temperament and personality functions, b144 Memory Functions,* and *d845 Acquiring, keeping, and terminating a job*), but were not added to the Core Set. The remaining 22 ICF categories were identified by 25 items from the DT/PL, and were excluded from further linking (Supplementary Table B).

TABLE 3. Additional properties of the QLACS, DT/PL, and IOCv2 questionnaires

Questionnaire*	Negative domains	Number of negative items	Positive domains	Number of positive items	Number of items to be linked
QLACS	Cancer specific		Cancer specific	4	39
	1. Appearance concerns	4	1. Benefits of cancer		
	2. Financial problems	4			
	3. Distress over recurrence	4			
	4. Family-related distress	3			
	Quality of Life		Quality of Life		
	1. Negative feelings	4	1. Positive feelings	4	
	2. Cognitive problems	4			
	3. Sexual problems	4			
	4. Physical pain	4			
	5. Fatigue	4			
	6. Social avoidance	4			
DT/PL	Generic domains		None	0	47
	1. Practical problems	7			
	2. Family/social problems	3			
	3. Emotional problems	10			
	4. Religion/spiritual concerns	2			
	5. Physical problems	25			
IOCv2	Negative impact scale		Positive impact scale		30
	1. Appearance concerns	3	1. Altruism and empathy	4	
	2. Body changes	3	2. Health awareness	4	
	3. Life interferences	7	3. Meaning of cancer	5	
	4. Worry	7	4. Positive self-evaluation	4	
	Additional subscales				
	1. Employment concerns	3			
	2. Relationship concerns	7			

All questionnaires consist of 47 items. *QLACS* = Quality of Life in Adult Cancer Survivors questionnaire, = Dutch version of the Distress Thermometer and Problem List, *IOCv2* = Impact of Cancer version 2 questionnaire.

TABLE 4. Final version of the Cancer Survivor Core Set with content validity percentages per cancer panel and association with the QLACS, DT/PL, and IOCv2 questionnaires

ICF category		Lung cancer (%)[a]	Colorectal cancer (%)[a]	Breast cancer (%)[a]	QLACS[b] k=39	DT/PL[b] k=47	IOCv2[b] k=30
Body Functions and Structures							
Mental functions							
b130	Energy and drive functions[c]	33	57	50	-	-	-
b140	Attention functions	83	86	75	2	1	-
b152	Emotional functions	100	100	100	13	6	11
Sensory functions and pain							
b280	Sensation of pain	100	71	100	4	1	-
Genitourinary and reproductive functions							
b640	Sexual functions	83	86	100	4	1	-
Activities and Participation							
Learning and applying knowledge							
d166	Reading[d]	68 (70)	76	70	-	-	-
d177	Making decisions	88	81	83	-	-	1
General tasks and demands							
d240	Handling stress and other psychological demands	100	95	93	-	-	-
Mobility							
d475	Driving[d]	84	71	67 (82)	-	-	-
Self-care							
d570	Looking after one's health[d]	100	86	83	-	-	1
Interpersonal interactions and relationships							
d710	Basic interpersonal interactions[d]	88	81	83	3	-	1
d720	Complex interpersonal interactions[d]	76	86	80	2	3	8
Major life areas							
d870	Economic self-sufficiency[d]	100	86	83	3	1	-
Environmental Factors							
Products and technology							

TABLE 4. Continued

ICF category		Lung cancer (%)[a]	Colorectal cancer (%)[a]	Breast cancer (%)[a]	QLACS[b] k=39	DT/PL[b] k=47	IOCv2[b] k=30
e310	Immediate family	100	95	100	-	1	-
e320	Friends	100	91	97	-	-	-
e355	Health professionals	96	100	90	-	-	-
Attitudes							
e410	Individual attitudes of immediate family members[d]	64 (70)	71	77	-	-	-
Services, systems, and policies							
e570	Social security series, systems, and policies[d]	88	86	97	-	-	-
e580	Health services, systems, and policies[d]	96	91	100	1	1	1
Items linked to other ICF categories		-	-	-	6	5	7
Non-linkable items		-	-	-	1	1	1
Short-term items		-	-	-	0	26	0

a Percentages displayed between brackets depict the CVI of only the lay experts subpanel
b Number of linked items (k=) is displayed. The digit indicates the number of items addressing the respective ICF category while a dash indicates this ICF category was not covered by the respective questionnaire
c This ICF category was added after establishing content validity by the described linking procedure. The number of items linked to this ICF category is included under 'items linked to other categories'
d This ICF category was added by the lay experts subpanel throughout the Delphi study

Non-linkable items

Three items (one per questionnaire) were not linkable to ICF categories. The items from the QLACS and DT/PL questionnaires focused on body image in cancer survivors, and the IOCv2 item involved an enumeration of related ongoing cancer- and treatment-related symptoms.

Unidentified ICF categories

Seven ICF categories from the initial Core Set were not covered by any of the questionnaire items: three from the Activities and Participation component and four from the Environmental Factors component (Table 4).

Final Cancer Survivor Core Set

The final version of the Cancer Survivor Core Set consisted of 19 ICF categories: 5 (26%) from the Body Functions and Structures component, 8 (42%) from the Activities and Participation component, and 6 (32%) from the Environmental Factors component.

DISCUSSION

In the current study, we aimed to develop and validate a core set representing the most relevant health-related problems of adults surviving cancer for more than one year after diagnosis. This led to the creation of the Cancer Survivor Core Set, consisting of 19 ICF categories. To the best of our knowledge, no other study has used the ICF to develop a core set generic for cancer survivors. The selected ICF categories in our Core Set represent the most relevant health-related problems of cancer survivors from a broad perspective. Moreover, we explicitly prioritized the patients' perspective, which resulted the addition of several ICF categories in the Delphi study. Although we realize that the cancer survivorship experience most likely consists of a balance between positive and negative impacts, we have decided to only identify the health-related problems in cancer survivors in the current study since we felt that these may significantly hamper a persons' functioning and require adequate attention from health-care providers.

Only one ICF category was added to the Core Set in the validation study, indicating that the experts selected a credible sample of health-related problems experienced by cancer survivors. In addition, it was possible to link 70 questionnaire items to the initial Core Set, further supporting this notion. In contrast, the fact that seven ICF categories in the initial Core Set were not covered by existing questionnaire items may indicate that important issues of cancer survivorship are not always identified by current questionnaires.

Compared with earlier studies in which core sets were developed, we selected a considerably smaller number of ICF categories.[12,22,23,29] A possible reason for this is that we aimed to identify the most relevant ICF categories for a broad yet concise reflection of relevant health problems. Consequently, we applied strict inclusion criteria for ICF categories to be eligible for inclusion in our Core Set. Moreover, the ICF categories were selected from the second level of detail (e.g. *B152 Emotional problems*), making them primarily relevant for identification. In clinical practice, further elaboration of an identified health-related problem will likely be needed.

A strength of this study is that we did not pre-select ICF categories. Moreover, we included a large, varied panel of experts, strengthening the validity of our results. The fact that written assessments were completed independently and anonymously ensured that experts could not influence each other.[17] The experts achieved a high level of consensus during the Delphi procedure by the second round. Because of this high level of consensus, there was no need for a third round.

A potential limitation is the drop-out rate between Delphi rounds (25%), which was unexpected and higher than that in similar studies.[22,23,30,31] A possible explanation is that some experts,

mainly lay experts, regarded the language in the ICF as too formal. However, we provided each ICF-category with the ICF-definition and the inclusion and exclusion criteria. In addition, we believe this loss of experts did not affect the overall diversity and proportions within and between the cancer panels in the second round. Another limitation is that our choice of panels may preclude generalizability to other cancers. However, limitation to the three cancers was based on expected prevalence rates and likely similarities in disease course.[19]

In conclusion, with the continued growth in the number of adult cancer survivors, the Cancer Survivor Core Set offers a valid yet concise reflection of the most relevant health-related problems in a general population of cancer survivors. However, although our results are promising, future studies are needed to confirm the generalizability of the Cancer Survivor Core Set in other settings and groups. The Core Set may be operationalized into a screening instrument to assess persistent health-related problems. Hereafter, targeted interventions may contribute to optimal and integrated care for adult cancer survivors.

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SUPPLEMENTS

SUPPLEMENTARY TABLE A. Overview of cancer survivorship questionnaires

Questionnaire	Number of items	Brief description	Reason for exclusion
Brief Cancer Impact Assessment - BCIA	16	Measures perceived functioning of long-term breast cancer survivors	Developed for breast cancer survivors
Cancer Problems in Living Scale - CPILS	29	Problem inventory of commonly faced problems to assess QoL in bone marrow transplant patients	Not available online
Cancer Survivors' Unmet Needs - CaSUN	42	Measures unmet needs and positive change in long-term survivors	Focus on unmet needs, not at health-related problems
Distress Thermometer and Problem List – DT/PL[a]	47	Short and long-term distress-screening instrument for consisting of the Distress Thermometer and Problem List, covering five life domains	*Included*
Impact of Cancer - IOC	41	Developed specifically to address long-term cancer survivorship and focuses almost exclusively on problems, issues, and changes	Updated version available
IOC version 2[b]	47	Refinement of the IOC questionnaire	*Included*
Long-term Quality of Life - LTQL	34	Tool to assess QoL in female cancer survivors based on a holistic QoL model	Focus on female cancer survivors
LTQOL-Breast Cancer	28	LTQL specific for breast cancer survivors	Developed for breast cancer survivors
Quality of Life Cancer Survivors - QoL-CS	41	Measures QoL in long-term cancer survivors and available in several languages	Not sufficiently validated
Quality of Life in Adult Cancer Survivors – QLACS[b]	47	Specific for cancer survivors and developed through in-depth interviews	*Included*
Satisfaction with Life Domains Scale for Cancer - SLDS-C	18	Derived from a previous scale and measures satisfaction with several life domains	Not sufficiently validated
UCLA-Prostate Cancer Index – UCLA-PCI	20	Developed to assess the impact of treatment for prostate cancer	Developed for prostate cancer
UCLA-PCI Survivors Module	46	Survivors module of the UCLA-PCI	Specific for prostate cancer survivors

a This questionnaire was added after the initial search. Since only few generic cancer survivorship measures exist we decided to also include one general cancer-related measure that is extensively used among cancer patients and survivors
b This questionnaire was included in the validation study and reason for exclusion is therefore not noted

SUPPLEMENTARY TABLE B. Excluded DT/PL items and linked ICF categories

DT/PL item	Linked ICF category	
Sleep	b134	Sleep functions
Dizziness	b240	Sensations associated with hearing and vestibular function
Taste	b250	Taste function
Nose dry/congested	b255	Smell function
Speech/talking	b320	Articulation functions
Fever	b435	Immunological system functions
Shortness of breath/breathing	b440	Respiration functions
Out of shape/condition	b455	Exercise tolerance functions
Constipation	b525	Defecation functions
Diarrhea	b525	Defecation functions
Weight change	b530	Weight maintenance functions
Feeling swollen	b535	Sensations associated with the digestive system
Nausea	b535	Sensations associated with the digestive system
Changes in urination	b620	Urination functions
Muscle strength	b730	Muscle power functions
Mouth sores	b810	Protective functions of the skin
Skin dry/itchy	b810	Protective functions of the skin
Tingling in hands/feet	b840	Sensations related to the skin
Daily activities	d230	Carrying out daily routine
Transportation	d470	Using transportation
Bathing/dressing	d510	Washing oneself
Eating	d550	Eating
Housing	d610	Acquiring a place to live
Housekeeping	d640	Doing housework
Meaning of life	d930	Religion and spirituality
Trust in God/religion	d930	Religion and spirituality

DTPL: Distress Thermometer and Problem List

IX

Chapter 9

Summary and general discussion

AIM OF THIS THESIS

The goal of this thesis was to better understand the impact of lung cancer and study how to integrate high-quality palliative/supportive care services for these patients throughout and after treatment. This was done using a combination of qualitative as well as quantitative studies. Further, it is important to note that several studies were conducted in a population of patients with a diversity of advanced cancers. This was based on the assumption that important lessons may also be drawn from other cancer populations. However, the primary goal is to present and discuss findings especially relevant to patients with lung cancer. Throughout this thesis, the World Health Organization (WHO) definition of palliative/supportive care was used. The WHO defines this line of care as "an approach to care that improves the quality of life of patients and their families through prevention and relief of suffering by means of early identification, assessment, and treatment of pain and other physical, psychosocial, or spiritual problems. It is not restricted to those near the end of life and should be offered to those patients living with and beyond cancer."[1]

In this chapter, we will first summarize our main findings. These findings will be highlighted specifically in the context of lung cancer, critically appraised, and compared to relevant literature. Several important methodological challenges inherent to the field of palliative/supportive care will then be outlined. Further, we describe the implications of our findings for the organization of healthcare (primary healthcare as well as hospital-based care), care providers, and researchers. We then present several generic challenges in the care for patients with advanced cancer (e.g. the optimization of advance care planning) as well for survivors of lung cancer. Last, we will outline the future directions for research as well as clinical care followed by our most important conclusions.

Summary of main findings

Lung cancer

In **chapter 2** we described the results of a systematic review regarding the effects of interventions facilitating shared-decision making for patients with lung cancer. Shared-decision making (SDM) is increasingly regarded as important and beneficial for patients, their loved ones, and clinicians to achieve care concordant with patients' personal preferences.[2] It can be defined as "a process to make decisions shared by both doctor and patients by informing patients using best evidence about risk and benefits, including patient-specific characteristics and values".[3] Since the process of SDM is likely to influence more than one outcome in the context of lung cancer, we decided to specifically focus on the impact on distress and health care utilization.

A systematic review was conducted and 12 studies, detailed in 13 publications, were included. The majority of patients included in these studies were diagnosed with advanced stage lung cancer. We observed no clear effects in studies measuring generic distress but found positive effects when studies employed anxiety- or depression-specific measures. Further, clear evidence for reductions in health care utilization, especially during the last three months of life, was observed in five studies. We conclude that facilitating SDM for patients with lung cancer likely leads to improved emotional outcomes (e.g. levels of depression) and the use of less aggressive therapies near the end of life (e.g. chemotherapy in the last month of life).

We subsequently reported on a randomized controlled trial conducted among patients who underwent systemic therapy and were diagnosed with lung cancer in **chapter 3.** The majority of patients (approximately 90% in both study groups) had stage 3 or 4 disease at study inclusion. We studied a novel approach to screen for distress and provide additional supportive care through routine completion as well as discussion of the Distress Thermometer (DT) and examined the effects on Quality of Life (QoL), mood, end-of-life care, and survival. The DT consists of a score (range 0 – 10) to indicate experienced distress in the past week and 47 questions covering five domains: practical, social, emotional, spiritual, and physical. In the Dutch setting, a DT-score >4 has been identified as the optimal cutoff score to indicate significant distress. Patients in the intervention group completed the DT at four time points: 1, 7, 13 and 25 weeks after randomization; patients in the control group did not complete the DT. Next, their response pattern was discussed with a psychosocial nurse and referral to other psychosocial or paramedical healthcare professionals was done, when indicated by the DT or specifically requested by patients.

In total, 223 patients with lung cancer were included, randomized and followed for up to 25 weeks. All patients were newly diagnosed with lung cancer or had a recurrence of their disease and started a form of systemic therapy (e.g. chemotherapy) at study inclusion. The mean change in the EORTC-QLQ-C30 global QoL-score between 1 and 25 weeks was

chosen as our primary outcome. A significant proportion of these patients either died (15%) or discontinued participation (35%) throughout the study period. The remaining 111 patients (50%) completed all four assessments. We observed no significant differences in QoL, mood or survival in the arm using the DT compared to those not using it. In an intention-to-treat analysis (approximated by linear mixed models analysis) we found similar findings. Yet, we did observe that fewer patients in the intervention group received aggressive care (e.g. hospital admissions in the last month of their life).

Although the findings of our trial were negative for the selected primary outcome (QOL), we proceeded to study the possible prognostic value of the score on the Distress Thermometer (DT-score) in identifying patients with lung cancer at risk for poor outcomes in **chapter 4**. All patients randomized to the intervention group of this trial (n=110) were included in this study.

Five known relevant predictors for survival were selected based on the literature and expert opinion, fitted in a Cox proportional hazards model, and combined with the reported DT-score at study inclusion. We observed that patients with a high DT-score (>4) experienced a lower QoL, more symptoms of anxiety and depression, and lived significantly shorter than patients who did not experience significant levels of distress. Importantly, this finding could not be explained due to significant differences in sociodemographic or clinical characteristics. Addition of the DT-score also significantly improved the predictive accuracy as well as the discriminatory value of the prediction models for one-year survival. This was further illustrated through a higher proportion (28% vs. 8%) of patients that was correctly classified as high risk (85%) of dying within one year after addition of the DT-score to the prediction model. Altogether, these findings suggest that use of a short and patient-centered screening tool, such as the DT-score, allows clinicians to correctly identify those patients with advanced lung cancer at risk for poor outcomes.

Conversations between oncologists and patients with advanced cancer

The subsequent two chapters focused on patients with various types of advanced cancer including patients with lung cancer. Conversations between patients with advanced cancer and their oncologist are perhaps one of the most central and important elements of care. Most of these conversations, especially in the setting of oncology, take place behind closed doors and have not been adequately studied.[4,5] In **chapter 5,** we therefore reported on a qualitative study based on 25 audio-recorded conversations between oncologists and their patients with advanced cancer. The outcomes of the cluster randomized controlled trial from which we obtained this data are presented in **Appendix I.** In our qualitative study, we aimed to characterize these conversations using a descriptive analysis and subsequently identified opportunities for care improvement. All oncologists participating in this study were trained

to use an evidence-based conversation framework: The Serious Illness Conversation Guide.[6,7] This guide provides the clinician with a framework used to assess a patient's values and goals (e.g. "If your health situation worsens, what are your most important goals?").

We derived five key themes from our data using a thematic analysis: 1) supportive dialogue between patients and clinicians; 2) patients' openness to discuss emotionally challenging topics; 3) patients' willingness to articulate preferences regarding life-sustaining treatments; 4) clinicians' difficulty in responding to emotional or ambiguous patient statements; and 5) challenges in discussing prognosis. These themes suggest that patients with advanced cancer are largely open to discussing personal values and goals with their oncologist. However, oncologists often struggle in adequately formulating a prognosis and may not always respond to expressed ambiguity or emotional statements. We therefore concluded that such skills should be targeted early in the clinical training of future oncologists in order to optimize the quality and timing of these conversations.

In addition to training oncologists to have earlier and high-quality conversations, information obtained throughout these conversations must also be documented in a clear and concise manner. In **chapter 6,** we reported on the concordance of these audio-recorded conversations with available clinician documentation in the electronic health record (EHR). Our goal was to examine the extent to which the documentation of serious illness communication reflects the content and nuances of these important conversations.

We reviewed all of the 25 audio-recorded conversations and compared the audio-recordings with corresponding clinician documentation in a pre-specified EHR template as well as free text progress notes. We then rated the degree of concordance. Our results suggested that concordance between clinician documentation and the actual conversation was best when documenting matters pertaining to family or specific goals. We observed the highest rate of erroneous documentation when clinicians documented prognostic information.

Overall, the degree of concordance was better when the template was used compared to when the conversations were only documented using a progress note. These findings suggest that the combined use of a pre-specified EHR template as well as a conversation guide to aid clinicians is promising to improve documentation of care for patients with advanced cancer.

Survivorship care

The number of patients with lung cancer living extended periods after their diagnosis has vastly increased in recent year due to recent treatment advances. In line with this, care for this patient population has become very important yet complex. In **chapter 7**, we therefore focused on cancer survivorship, contrasted this emerging field to palliative care by way of a commentary

article. We conclude that there is a significant overlap between both care fields. This overlap is especially pronounced when describing the 1) confusion on terminology; 2) care being interdisciplinary and involving multiple specialists; 3) lack of consensus on an optimal model of care provision; 4) goals of treatment (e.g. symptom relief); 5) increasing demands on the workforce in the coming years and 6) a clear need for quality metrics to measure the quality of provided care. From these six observations, we continued to identify and outline several important opportunities for shared and actionable steps in research and policy discussions for both care fields.

In **chapter 8** we subsequently describe the design and validation of a generic tool to capture the most important health-related problems of adult cancer survivors after treatment. Three expert panels were selected based on the current and projected rates of cancer survivors who are negatively affected by health-related problems. Although various definitions of cancer survivors exist, we opted to define a cancer survivor as "patients living more than one year after their diagnosis".[8] Experts on lung cancer, breast cancer, and colorectal cancer were invited to participate. Each panel consisted of lay experts (e.g. patients), medical professionals (e.g. clinicians), and other healthcare workers (e.g. psychologists). We used the available categories of the International Classification of Functioning, Disability, and Health (ICF) as a basis for the development of this tool.[9]

We proceeded to include a total of 101 experts in a Delphi study and asked these experts to select the ICF categories representing the most relevant and persistent issues for cancer survivors. Throughout two Delphi rounds, these experts reached consensus on 18 ICF categories. One additional category was added after validating the set of categories using three validated cancer survivorship questionnaires. The final "Cancer Survivor Core Set" consisted of 19 ICF categories and likely represents the most relevant issues for adult cancer survivors. Although further validation and optimization is needed, this tool can be used to personalize care for cancer survivors by functioning as an instrument to screen for and target important concerns that patients living with or beyond their (lung) cancer diagnosis may have.

Critical appraisal

Defining high-quality care

Lung cancer remains a devastating diagnosis to receive for patients and their loved ones. The content of this thesis is likely a timely effort since both the American Society of Clinical Oncology and the European Society of Medical Oncology have recently released position papers on the integration of supportive care services in routine oncology practice.[10,11] Although not specific to lung cancer, both of these position papers conclude that: "Together with anticancer therapies, medical oncology should encompass patient-centered care by providing supportive

and palliative interventions at all stages of the disease". In addition to this, the World Health Organization (WHO) has recently stressed that "lack of training and awareness of palliative care among medical professionals is a major barrier to improving access" but also that "early palliative care reduces unnecessary hospital admissions and the use of health services".[12]

Integration of palliative/supportive care

Early and routine integration of palliative/supportive care is feasible and important for patients with lung cancer from the time of diagnosis until the end of life. A number of landmark studies, although primarily conducted in the United States and Canada and across a variety of patients with advanced cancer, have provided clear evidence through several well-conducted clinical trials.[13–15] To summarize, the majority of studies observed clear improvements in QoL, emotional outcomes such as anxiety or depression, and reductions in healthcare utilization when palliative/supportive care was structurally embedded early throughout the illness trajectory. Until recently no data from European countries was available to provide similar results. Fortunately, a thoroughly designed cluster randomized trial from Belgium including 186 patients with a diagnosis of advanced solid cancer was recently published.[16] Approximately 30 percent of patients in both study groups had received a diagnosis of lung cancer. This study, in line with the studies conducted in the United States and Canada, showed that early and systematic integration of palliative care leads to an improved QoL for patients.

In the randomized trial included in this thesis (Chapter 3) we focused on a population of patients with lung cancer who underwent systemic therapy. The majority of patient, approximately 90 percent, was diagnosed with advanced stage lung cancer. Unfortunately, we did not observe improvements in QoL, anxiety, depression, or patient satisfaction. Our intervention did impact care received near the end of life which has been identified as an important hallmark to assess the quality of care.[17,18] These largely negative findings do not undermine the importance of timely and structural palliative care in this patient population for several reasons. First, since patient satisfaction was high throughout the entire study and in both study arms, a ceiling effect may have obscured likely benefits of our intervention. Additionally, a significant proportion of patients dropped out of the study and participant recruitment was particularly challenging. These issues point to the issue of recruitment and retainment of participants in palliative care settings.[19] Compared to similar studies, our follow-up period was relatively long (25 weeks vs. 12 weeks) and all patients recently started a form of systemic therapy. Although this allowed us to study a relatively homogenous study population, side-effects of treatment may have further obscured potential benefits of our intervention. This is especially relevant since our primary outcome measured health-related QoL. Future studies should therefore chose their primary outcome, preferably a disease-specific measure of well-being, with care and specifically report on their follow-up period and the rationale for this.

Shared decision making and patient-reported outcome measures

The concept of shared-decision making was identified as important to patients with advanced lung cancer as it likely leads to improved health outcomes through reductions in distress as well as healthcare utilization (chapter 2). In line with this, the topic has gained increased attention across different settings and diseases.[20–22] Importantly, patients likely differ in their communication preference (e.g. patient-driven, clinician-driven, or truly shared).[2,23,24] Discovering and adhering to this preference is at the core of shared-decision making.[21] Decision-aids, although relatively well-established in other fields of medicine,[25,26] do not yet have a central role in the care for patients with advanced lung cancer. Although several promising studies are underway[27–29] there is likely still a long way to go before these tools will be implemented in clinical practice. The development and implementation of such aids may make it easier for oncologists to navigate the increasingly complex treatment landscape together with patients and their loved ones.

Further, we show that those patients with advanced lung cancer at risk for poor outcomes may be timely identified through use of a short and patient-centered screening tool. This is in line with the recommendation that patient-reported outcome measures (PROMs) should be routinely integrated in oncological care as this likely leads to improvements in QoL, reductions in healthcare utilization and even prolonged survival.[30,31] Use of the "surprise question" (Would I be surprised if this patient died in the next year?) may earlier identify those patients in need of palliative/supportive care and also yields important prognostic information regarding survival.[32] As such, combining this question with a validated PROM (such as the DT-score) that may yield similar prognostic information is a promising option to timely and correctly identify those patients with advanced lung cancer in need of additional support.

Methodological challenges

Several notable methodological challenges pertaining to research and clinical implementation in the field of palliative/supportive care exist. At least four key issues are likely to be of importance in the context of this thesis: 1) lack of a standard definition of palliative/supportive care; 2) patient inclusion; 3) lack of funding; and 4) misconceptions by the public and other healthcare professionals. Each of these challenges will be briefly outlined below. Although most of these challenges will likely remain throughout the coming decade, they are important factors to bear in mind when conducting research in the field or trying to implement new strategies to support the early integration of supportive care services.

Lack of a standard definition

The lack of a standard definition in palliative oncology care is troublesome and has previously been confirmed through an elaborate review of 1213 scientific articles.[33] The authors conclude

that the definition likely depends on the type of setting (e.g. oncology vs. palliative care) and that there were up to 16 different iterations of "palliative care". Having a standard definition would be a first and important step to compare different settings and make sustainable and lasting changes. In addition, a standard and shared definition likely leads to comparability across different settings in terms of the provision of "usual care". Currently, this is an important limitation when comparing randomized trials on integrated palliative care from various settings or countries as was also observed in our systematic review and our RCT.[34–37] The previously described WHO definition of palliative/supportive care as "an approach to care that improves the quality of life of patients and their families through prevention and relief of suffering by means of early identification, assessment, and treatment of pain and other physical, psychosocial, or spiritual problems that is not restricted to those near the end of life and should be offered to those patients living with and beyond cancer"[1] was used throughout this thesis and likely provides a good starting point.

Patient inclusion

As we experienced in our RCT, patient inclusion is notoriously difficult in the setting of palliative care and in the field of survivorship care.[19,36,38] Several ethical considerations related to minimizing risks and burdens to patients are important to take into account when conducting research in this sphere.[39,40] The study inclusion period is often long, the study samples may be too small, and a significant number of patients likely drop-out throughout the study. Although the mainstay of evidence is still derived from randomized controlled trials, one might question whether this is the most optimal way to conduct research. Well-designed observational studies or cross-sectional surveys may also provide valuable information and a pragmatic approach is often needed to conduct valid research in the field.[10]

Funding

Another important limitation to consider is the lack of funding by government or other agencies. Although the Dutch government has recently made up to € 50 million available to stimulate research and the uptake of supportive care services, this amount is relatively small when compared to funding available for trials of drugs or druggable targets in experimental and fundamental oncology that are often funded by the pharmaceutical industry. This is an important concern, both nationally and internationally, and it is important to realize this when applying for funding or studying strategies to routinely embed supportive care services.[41] Increased (inter)national collaboration between different research groups and public institutions may allow for enhanced funding opportunities and also provide direct societal impact.

Public perception

Last, a recent poll conducted by the Dutch government concluded that only 34 percent of Dutch residents are familiar with the concept of palliative care.[42] Internationally, this finding is further confirmed through a well-conducted qualitative study interviewing 48 patients and 23 caregivers.[43] From the study, the authors conclude that "there is a strong stigma attached to palliative care" and "that education of the public, patients, and health care providers is paramount for early integration to be successful". This belief, although likely changing over the coming years, may also persist among practicing clinicians.[44,45] These are not surprising findings considering that palliative care is a relatively new specialty and not all clinicians may be familiar with it. In addition, talking about death or issues near the end of life, as an important hallmark of palliative care, may be a societal issue that requires time, campaigns targeting public perception, and open conversations to gradually make this a more acceptable topic.

Implications of our findings

Earlier and better conversations

In line with chapters 5 and 6, high-quality conversations between oncologists and patients with cancer are vitally important to enable care concordant with patients' preferences. Advance care planning (ACP) lies at the center of earlier and better conversations but is often viewed as a broad and relatively vague concept. Historically, completion of an advance directive or a similar legal document was at the core of this process. This process alone has proven to be inefficient in achieving that patients receive the care they want near the end of life.[46–48] In recent years, the definition of ACP has therefore been expanded and can now be summarized as: "the ability to enable individuals to define goals and preferences for future medical treatment and care, to discuss these goals and preferences with family and health-care providers, and to record and review these preferences if appropriate".[49] Experienced barriers are related to the timing of these conversations, the most appropriate way to introduce them to patients, and issues regarding the documentation of these conversations.[5,6,50]

Training oncologists and other clinicians to have conversations with their patients regarding ACP, personal values, and their goals is another important facet to explore. Results of this thesis (chapter 5) show that oncologists generally respond well to a brief communication training, the use of an evidence-based guide, and system triggers (e.g. e-mail reminders) to enable these conversation.[7,51–53] Although oncologists likely require further training with regards to prognostication and in recognizing and responding to emotional cues, the use of a tool such as the Serious Illness Conversation Guide is feasible and successful in reducing patient's anxiety and distress.[52,53] Moreover, previous work has provided evidence that prognostic communication does not take away hope and likely strengthens the therapeutic relationship between clinicians and their patient.[54,55]

Accurately documenting ACP conversations (chapter 6) is another salient issue in order to timely communicate preferences in times of need (e.g. when a patient visits the emergency department).[56,57] Having information regarding such preferences available likely leads to care concordant with patients personal preferences.[58] Apart from a feasibility study with promising results,[59] no specific module to document ACP conversations exists in Dutch hospitals. Development and nationwide availability of such a tool should be a first step to allow oncologists to streamline their documentation in a concise yet inclusive manner and convey the most important information. More importantly perhaps, relevant documentation should be made available to all healthcare providers including those working in primary care. Realizing that the information is dynamic since preferences likely change over time should be taken into account when designing tools to capture and document patient preferences regarding their future care.

Overcoming barriers

There are still major barriers to overcome in order to meet the needs of all patients with advanced lung cancer. In the majority of Dutch hospitals, patients with advanced lung cancer are cared for by a multidisciplinary team consisting of several medical specialists (e.g. radiotherapists, surgeons and pulmonary oncologists). Naturally, not every patient requires the expertise from all professionals but hospitals likely have resources available should the need for additional support beyond medical treatment arise throughout or after treatment. Although clinicians always intend to provide the best possible care to all patients this is not always enabled by the health system in which they work.[10] Time constraints, individual attitudes and lack of expertise, as well as misconceptions regarding palliative care or a lack of education regarding such care are important elements factoring into this.[60]

This is further illustrated in two recent reports.[61,62] A Dutch survey among 654 patients with incurable cancer concluded that approximately one-third of patients felt "abandoned by their clinician" after hearing that cure was no longer possible. Researchers from the UK Royal College of Physicians also concluded that "patients with advanced cancer want proactive conversations about their future" and that "these discussions are fundamental to effective clinical management plans". Further, this report highlights the professional reluctance to engage with patients about these important topics.

Early training

Why is quality of care near the end-of-life lacking and do many patients with advanced lung cancer receive care discordant with their preferences?[63–66] One important explanation may be that teaching medical students about care near the end of life is not adequately embedded in medical curricula, as shown by a recent study conducted across the Netherlands.[67] Although these skills may often be viewed as "soft skills" by clinicians and medical students alike, such

competencies are likely of vital importance to all areas of medicine. Teaching medical students how to provide excellent patient-centered palliative/supportive care based on the most recent available data is therefore of vital importance to further expedite the field and may also significantly impact the quality of oncological care in the coming years.

Identifying a model for implementation

Consensus is needed on the best approach to integrate palliative/supportive care within routine clinical care for patients with advanced lung cancer. The Dutch guideline on "Detection of Need for Care"[68] stipulates a careful process in which the surprise question is used to identify the appropriate patient population and to screen this group regularly with the Distress Thermometer to asses experienced problems and the need for timely referral to other health care professionals. This guideline is gradually being implemented across a range of different hospitals in the Netherlands but uptake across all care settings is still lacking. Routine and preferably digital implementation of a patient-centered tool, such as the DT, is a relatively easy measure to implement and should be considered.

Internationally, several models to enhance the integration of palliative/supportive care have been promulgated. These vary from providing supportive care at home, specialized palliative care teams within the hospital or "on-demand" supportive care (either at home or in the hospital) as identified by the patient or their loved ones.[69] Although a unified model will likely require various iterations and may not be due for a long time, health care providers can learn from each other throughout the process and adapt their standard of practice accordingly.

Survivorship care

As outlined in chapters 7 and 8, the care for patients living with or beyond lung cancer is becoming increasingly relevant yet complex.[70,71] The growing uptake of screening programs will likely increase the number of patients diagnosed with early-stage disease in the coming years and significantly improve the five-year survival rate. Although lung cancer is still the primary cause of cancer-related mortality in the Western world, recent advances in treatment options have made the issue of metastatic-cancer survivorship especially pertinent for patients with lung cancer.[72–79] This changing face of lung cancer requires clinicians to rethink the care for these patients beyond the first period after a diagnosis.[80] This is further illustrated through a recently published opinion article that stressed the importance of studying survivorship among metastatic-cancer survivors.[81] This report states that the majority of current research is restricted to patients who are in remission and only address issues that may arise after patients complete their cancer treatment.

A first and important step would be to screen lung cancer survivors for persistent problems in the years after their diagnosis.[82,83] The Institute of Medicine has defined four essential elements

of survivorship care (1) surveillance for the recurrence of cancer, new primary cancers, and medical and psychosocial late effects; (2) prevention of recurrent or new cancers and of late effects of treatment; (3) intervention for consequences of cancer and treatment; and (4) coordination between oncology specialists and primary care clinicians.[84,85] Specific strategies that may be considered for lung cancer survivors are outlined in Figure 1.[80]

FIGURE 1. Summary of potential long-term treatment strategies for lung cancer survivors. Adapted from Vijayvergia et al: Survivorship in Non–Small Cell Lung Cancer: Challenges Faced and Steps Forward.

QOL Factor/ Symptom	Recommendations for Management
Fatigue	• Assess for underlying pulmonary dysfunction/disease, depression, thyroid dysfunction • Encourage routine physical activity as tolerated
Pain	• NSAIDS, opioids, antidepressants, antiepileptics as needed • Consider referral to physical therapy • Early referral to pain management
Peripheral neuropathy	• Duloxetine, pregabalin, NSAIDs, opioids
Psychosocial and economic issues	• Screen for anxiety and depression at regular intervals • Screen for comorbidities and socioeconomic factors • Consider pharmacologic interventions (e.g. antidepressants) • Referral to mental health professional, cognitive-behavioral therapy, peer support programs, educational-informational programs as appropriate/available • Regular assessment of practical and financial concerns
Tobacco use	• Assess for continued tobacco dependence at regular intervals • Combination behavioral and pharmacologic interventions • Referral to tobacco cessation programs
Respiratory dysfunction/dyspnea	• Bronchodilators as indicated • Supplemental oxygen as indicated • Consider referral to pulmonary rehabilitation program
Sedentary lifestyle/lack of physical activity	• Assess pretreatment and posttreatment physical activity level • Counsel against inactivity/sedentary lifestyle • Encourage routine physical activity (30 min/d most days of the week) as tolerated • Consider referral to rehabilitation program (physical therapy, pulmonary rehabilitation, exercise specialist)
Preventive health (vaccinations)	• Review vaccination history at regular intervals • Annual influenza vaccination • Pneumococcal vaccination as per guidelines • Immunization Schedule
Recurrence/Second malignancy	• Surveillance for recurrence with regularly scheduled clinical evaluations (e.g. physical examination, imaging) • Screen for continued tobacco use and encouraged cessation as needed

The ideal time to start thinking about survivorship issues in lung cancer care has not yet been identified. Yet, lung cancer affects patients and their families in a multitude of ways and a diagnosis often has lasting effects on their well-being. Primary care, by way of the general practitioner, plays a vitally important role in the provision and continuity of this care.[86] Shared survivorship care can be defined as "a joint participation of general practitioners and specialists in the planned delivery of care for patients with a chronic condition".[87] Such models, often using survivorship care plans as a vehicle to coordinate shared care, have been implemented across a number of different cancer populations. Although other cancer survivors clearly indicate the need for such models,[88] data on efficacy is inconsistent or lacking.[89–92] Additional research is needed to identify the potential of these models for lung cancer survivors as well as further refinement of available tools to timely identify persistent issues among lung cancer survivors.

Future directions

Choosing appropriate outcome measures

There are several important future directions to outline. More evidence on the effects of different strategies to embed palliative/supportive care on important health outcomes such as QoL, anxiety, depression, and healthcare utilization near the end of life is needed. Future studies, preferably conducted in a European context, should also consider including broad patient-centered outcomes such as well-being[93]. More robust outcome measures that focus on capturing the quality of care, such as the receipt of goal-concordant care or aggressiveness of care near the end of life, should also be considered.[17,94,95] Although such outcome measures are difficult to truly capture, efforts to streamline the measurements are well underway.[94] Moreover, the level of "standard care" should be comparable across studies and replicability of similar interventions is of importance.

Caregivers

The role of caregivers and possible stresses associated with caregiving has also gained increased attention in recent years.[96,97] Caring for patients with advanced cancer is a difficult period for loved ones and studies have observed a considerably higher incidence of depression among cancer patient caregivers.[97] This has led to increased attention for the physical and psychosocial well-being of caregivers. In this context, it is important to realize that the role of caregiver likely shifts over time and that a variety of caregivers may support patients throughout their illness. Although the studies in this thesis do not include caregiver-related outcomes, future studies should include such outcomes to identify potential stressors, and to provide evidence to further tailor care to their specific needs.[98]

Palliative care beyond oncology

The majority of evidence supporting the routine integration of palliative/supportive care is derived from studies in oncological settings. Yet, serious illness and palliative/supportive care is not restricted to oncology. Diagnoses such as advanced COPD, interstitial lung diseases, advanced heart failure, and chronic kidney disease are equally devastating but clinicians often struggle in finding the right time to talk about supportive or palliative care.

This may be due to the unpredictability of the disease course, especially when contrasted to lung cancer and the majority of other oncological diagnoses. The surprise question has been suggested as a valid identification tool for patients with COPD and patients with heart failure although it should likely be combined with other outcomes such as the Clinical COPD Questionnaire.[99–101] In addition, the recently developed Supportive and Palliative Care Indicators Tool[102] provides care providers with a set of indicators to detect whether patients are in need of palliative care (e.g. a recent hospital admission or emergency department visit) and can be useful in a variety of care settings.

Conclusions

We aimed to outline and explore the impact of a lung cancer diagnosis and suggest venues for the early and systematic adoption of palliative and supportive care services. Palliative/supportive care is a rapidly expanding field and is paramount to provide optimal and patient-centered lung cancer care. As shown throughout this thesis, many opportunities to enhance integration of this line of care within routine medical care exist. The routine use of patient-centered PROMs should be advocated, and possibly combined with the surprise question, to timely identify those patients with lung cancer in need of additional support. No exact model has been identified but experts in palliative care should be available in all care settings and, more importantly, be consulted early and in a systematic manner. Truly shared conversations between (pulmonary) oncologists, general practitioners and their patients regarding ACP, patients' personal preferences, values and goals is another vital hallmark of palliative/supportive care. Realizing that communication with seriously ill patients is difficult but that these skills are teachable and that not all patients may want to have these conversations with every healthcare providers is an important first step. In addition, shared documentation of such conversations across healthcare settings and providers will be of utmost importance in order to provide care concordant with personal patient preferences and improved health outcomes. Further, training early-career clinicians or medical students to have these conversations, ideally through the use of evidence-based tools and trainings, is an important aim for the future.

Throughout all this, primary care plays a vitally important role. Clear and timely communication between healthcare providers using a centralized form of documentation will strengthen this transition. Last, the population of patients living with metastatic lung cancer (metastatic-cancer

survivors) or patients living beyond lung cancer is rapidly expanding. Survivorship issues for these patients are becoming increasingly relevant and should be identified and targeted early. A combination of these strategies, possibly paired with an increase in available funding as well as campaigns to enhance public perception of palliative and survivorship care, will lead to improved personal and patient-centered care for all patients living with and beyond lung cancer.

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A–I

Appendix I

Impact of the Serious Illness Care Program: Results of a randomized controlled trial in outpatient oncology

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ABSTRACT

Importance: High-quality conversations between clinicians and seriously ill patients about values and goals are associated with improved outcomes but occur infrequently.

Objective: To examine feasibility, acceptability, and effectiveness of a communication quality-improvement intervention (Serious Illness Care Program, SICP) on patient outcomes.

Design, Setting, Participants: Cluster-randomized controlled trial of SICP in outpatient oncology. Patients with advanced cancer and oncology clinicians participated between September 2012 and June 2016.

Intervention: The intervention included tools, training, and system changes.

Main outcomes and Measures: The co-primary outcomes included goal-concordant care (Life Priorities) and peacefulness (PEACE) at the end of life. Secondary outcomes included therapeutic alliance (Human Connection Scale), anxiety (GAD-7), depression (PHQ-9), and survival. We evaluated uptake and effectiveness of clinician training, clinician adoption of the conversation tool, and conversation duration.

Results: We analyzed data from 91 clinicians in 41 clusters (72% participation, 48 intervention, 43 control) and 278 patients (46% participation, 134 intervention, 144 control). Clinicians (47/48) rated the training as effective (4.3/5, SD=0.7); of those who received a reminder, 87% completed at least one conversation (median duration 19 minutes, range 5-70). Peacefulness, therapeutic alliance, anxiety, and depression did not differ at baseline. We were only able to evaluate the co-primary outcomes in 64 patients; no differences were found between the intervention and control groups. However, the trial demonstrated significant reductions in the proportion of patients with moderate-severe anxiety (10% vs. 5% (p=0.05)) and depression symptoms (21% vs. 11% (p=0.04) in the intervention group at 14 weeks after baseline. Anxiety reduction was sustained at 24 weeks (10.4% vs. 4.2%, p=0.02), while depression reduction was not sustained (18% vs. 13%, p=0.31). Survival and therapeutic alliance did not differ between groups.

Conclusions: The results of this cluster-randomized trial were null with respect to the co-primary outcomes of goal-concordant care and peacefulness at the end of life. Methodologic challenges for the primary outcomes, including measure selection and sample size, limited the conclusions that can be drawn from the study. However, the significant reductions in anxiety and depression in the intervention group are clinically meaningful and require further study.

Trial Registration: Registered with ClinicalTrials.gov (NCT01786811), available at www.clinicaltrials.gov.

BACKGROUND

In the last year of life, patients with serious illness suffer with physical and emotional distress, inadequate communication with clinicians, and medical interventions inconsistent with patient priorities and preferences.[1-7] Patients who discuss end-of-life care with their clinicians, especially earlier in the disease trajectory, are more likely to have positive outcomes, including better quality of life, less distress, and a higher likelihood of receiving care consistent with their preferences.[8-10] However, evidence indicates gaps in the frequency, timing, and quality of such conversations.[11-14] To address these deficiencies, national medical organizations have called for improved communication about patients' values, goals, and care preferences[15,16] ("Serious Illness conversations").

While palliative care clinicians train for this task, a limited palliative care workforce suggests the need for other clinicians to effectively lead serious illness conversations.[17,18-20] However, interventions seeking to equip non-palliative-care specialists to better communicate with patients about end-of-life concerns have not improved patient outcomes, such as psychological symptoms or quality of life. In fact, in one trial of trainee physicians, a communication training program was associated with an increase in patients' depressive symptoms, raising concerns that end-of-life conversations may worsen psychological symptoms.[25] Additionally, clinicians cite concerns about harming patients as a barrier to initiating these conversations.[26,27] Because non-palliative care clinicians must fill this gap in communication with patients, we systematically developed and extensively pilot-tested the Serious Illness Care Program (SICP) with clinicians and patients.[28]

This trial evaluated the feasibility and acceptability of our intervention (SICP) - including uptake and effectiveness of training, adoption of the conversation guide, and duration of conversations—and its impact on patient outcomes: goal-concordant care and peacefulness at the end of life (co-primary outcomes) and therapeutic alliance, anxiety, depression, and survival for the total population (secondary outcomes). We chose the measures of peacefulness and goal-concordant care because they are patient-centered, important to patients and caregivers, and do not make assumptions about patients' care preferences (life-prolonging vs. comfort-focused).

METHODS

Context

Dana Farber Cancer Institute (DFCI), an NCI-designated cancer center, in Boston, Massachusetts was the study site.

Intervention Description

The intervention included tools, training, and system changes.[28] Clinical tools included a clinician-facing Serious Illness Conversation Guide (SICG),[14] a patient letter introducing the SICG, and a Family Guide after the discussion.[28] Clinician training included a 2.5-hour interactive, skills-based training on the SICG delivered by palliative care experts who offered follow-up coaching. System changes included routine identification of patients at high risk of death, email reminders to initiate conversations ("reminders"), and a novel structured template in the electronic medical record (EMR) for SICG documentation. Control clinicians provided usual care; control patients did not receive supporting tools. Each clinician received a $150 gift card for participation. Patients and caregivers received no compensation for participation.

Trial Design

We employed a cluster randomized-controlled trial design from September 2012 to June 2016.

Participants

We invited clinicians (physicians (MD), physician assistants (PA), and nurse practitioners (NP)) from ten disease centers and two satellite clinics to enroll. We excluded gynecology-oncology clinicians (participating in a concurrent study on end-of-life care) and melanoma clinicians (pilot subjects). We defined clusters as units of clinicians within a disease center based on clinical workflow; a typical cluster included 1 NP/PA and 2-3 physicians. Cluster sizes varied. Enrolled oncology clinicians identified eligible patients by reviewing patient lists at regular intervals and answering the surprise question- "*Would I be surprised if this patient died in the next year?*"[29] Patients for whom clinicians responded "no" were eligible for participation. We excluded patients with cognitive impairment, non-English-speaking patients, and patients unable to identify a caregiver.

Outcomes

Patient Measures for Decedents

All patients completed a baseline survey at enrollment and follow-up surveys approximately every two months for two years or until death. Lacking a 'gold standard' for measuring the co-primary outcome of concordance between patient goals and care provided at the end of

life,[30] we developed two novel, patient-centered tools that did not pre-judge patient values: Life Priorities survey[28] for patients and the Family Perceptions survey.[28] Based on a list of nine common goals drawn from an extensive literature review and patient interviews, we asked patients to select and rank five goals in order of importance and following patient death, we asked caregivers whether each goal was fulfilled in the patient's final week and final three months of life.[7,9,31-34]

We assessed the co-primary outcome of peacefulness in decedents through the PEACE (Peace, Equanimity and Acceptance in the Cancer Experience) questionnaire, a validated tool yielding two subscales: Struggle with Illness, measuring feelings of upset, worry, unfairness, shame, and anger at diagnosis (7 questions, score range 7 to 28, Cronbach's alpha 0.81) and Peaceful Acceptance, measuring acceptance of diagnosis, inner calm, and feelings of being well-loved (5 questions, score range 5 to 20, Cronbach's alpha 0.78.)[35]

Patient Measures for Total Population

We measured therapeutic alliance (secondary outcome) with a modified version of The Human Connection (THC) scale, which evaluates patients' sense of mutual understanding, caring, and trust with their physicians.[36] To decrease patient burden and avoid redundancy, we included 7 of the original 16 items (Cronbach's alpha 0.90), a reduction supported by the tool developer (Mack and Bernacki, personal communication). Scores on this shortened THC range from 7 to 28 (Cronbach's alpha of 0.83 in this trial data). We assessed anxiety and depressive symptoms (secondary outcomes) using the Generalized Anxiety Disorder-7 Scale (GAD-7, 7 items, range 0 to 21, Cronbach's alpha 0.92) and the Patient Health Questionnaire 9 (PHQ-9, 9 items, range 0 to 27, Cronbach's alpha 0.86 to 0.89).[37,38] We defined scores in the moderate or severe category on both scales (10 or higher) as clinically significant.

We identified patient deaths from the Dana-Farber Clinical Operational and Research Information System database.[28]

Clinician Measures

At baseline, we surveyed clinicians in both arms about profession (MD, PA, NP), gender, years in practice, percentage clinical time, and disease center. After training, we surveyed clinicians for training effectiveness (Likert scale range 0-5). After sending a reminder, we surveyed clinicians for conversation occurrence and duration.

Randomization

We stratified clinician clusters by disease center or satellite facility, and within strata, randomized one-half of the clusters to the intervention (20) and one-half to control (21).

Blinding

Enrolled clinicians were not blinded to study arm. Patients were blinded to the study arm of their clinicians.

Sample Size

We performed power calculations for the study's primary outcomes. To ensure an overall 5% type I error rate, we used a 2.5% type I error rate for each of the two primary hypotheses. We based the power calculations on having 200 evaluable patients per study arm. We allowed for 6% un-evaluability due to patient dropout; however, we had significantly fewer evaluable patients than expected, prompting us to conduct a post-hoc power calculation. With 38 intervention patients and 26 control patients with goal-concordant care outcomes, a post-hoc power calculation found 25% power to detect at least a 0.6 higher mean on the intervention arm (a-priori specified clinically important increase). With 47 intervention and 47 control patients with the PEACE outcome, a post-hoc power calculation found 29% power to detect at least a 1.3 point higher mean score on the intervention arm (a-priori specified clinically important increase).

Statistical Analysis

We performed statistical analyses with SAS software, version 9.4 (SAS Institute, Cary NC). We used proportions for categorical variables and means/medians for continuous variables. All comparisons across study arms accounted for clustering of patients within clinician teams. We considered a p-value ≤ 0.05 as statistically significant. All analyses were conducted based on intention-to-treat.

Clinician and Patient Characteristics

When comparing baseline clinician and patient characteristics between arms, we used generalized estimating equations (GEE)[39], chi-square tests for categorical variables, and t-tests for continuous variables.

Patient Measures for Decedents

Goal-Concordant Care

We evaluated goal-concordant care by matching each decedent's final Life Priorities[28] survey (within three months of death) with their caregiver's Family Perception[28] survey. We scored each of the patient's three highest ranking goals as "concordant" if the caregiver indicated the goal had been achieved "to a large extent" resulting in a score of 0, 1, 2, or 3 goals met. We compared the arms using a GEE Wilcoxon rank-sum type score test for ordinal categorical data.[39]

Peacefulness

Using GEE chi-square tests for ordinal data, we compared both PEACE[35] subscales for decedents at baseline and at 3 months before death across the study arms.

Patient Measures for Total Population

Therapeutic Alliance, Anxiety, and Depression

We created a separate model for each outcome of interest, using a continuous score for therapeutic alliance, and dichotomizing anxiety[37] and depression[38] as moderate/severe versus none/mild. Due to variation in timing (patients did not complete surveys at the same fixed points), we fit repeated-measures models via GEE.[39,40] We calculated the mean therapeutic alliance score and logits of the probabilities of moderate/severe anxiety and moderate/severe depression as a cubic spline of time of survey, using all data on all patients from all time points in an intention-to-treat repeated-measures model.[41] We modeled the correlation between outcomes on the same patient at a pair of times as auto-regressive.[42] Because conversations occurred on average at 12 weeks after baseline in the intervention arm, we compared patient outcomes across study arms at 14 and 24 weeks after baseline (the average completion time for the next two surveys) using the estimated means and probabilities at these two time points from the repeated-measures models.

We fit separate spline models for control and intervention arms, allowing the trends to vary over time differently in each arm, and we used inverse propensity weighting to balance the three outcomes between the two arms at baseline to ensure that differences at later time points were not due to baseline differences (even though differences were non-significant at baseline). For each outcome, we modeled the propensity score (probability of being in the intervention arm) via logistic regression with baseline outcome (therapeutic alliance scores, anxiety, or depression), and patient characteristics as predictors. Although dropout and survival did not differ between arms, the models[40] protected against potential biases arising from patients in one arm being followed for longer time periods.

Survival

We obtained Kaplan-Meier 2-year survival estimates from date of baseline and used a log-rank test to compare survival differences between all enrolled intervention and control patients.

Ethics

The DFCI Institutional Review Board reviewed and approved the study; it is registered with clinicaltrials.gov (NCT01786811). All clinicians and patients provided written informed consent.

RESULTS

Sample Recruitment and Demographics

We enrolled 91 oncology clinicians, grouped into 41 randomized clusters (73% participation, Figure 1).

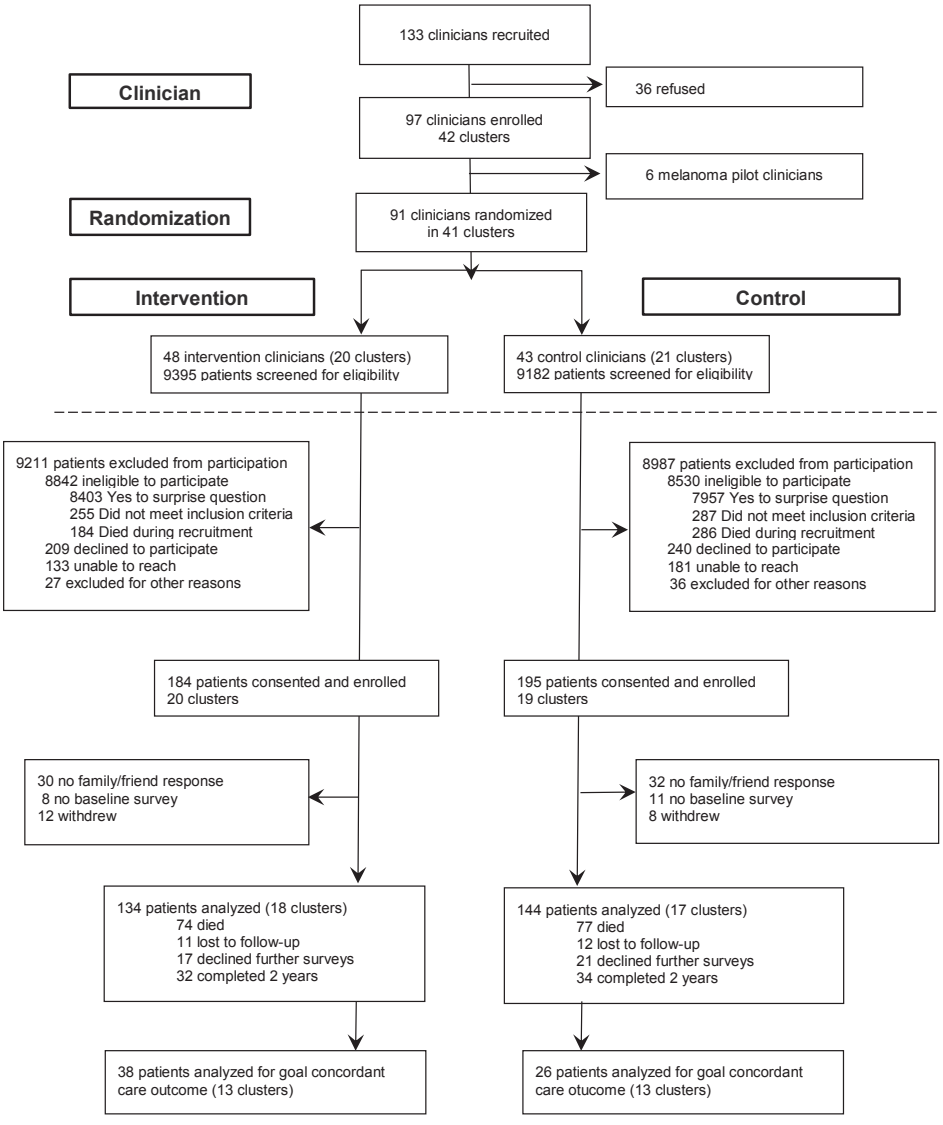

FIGURE 1: CONSORT Diagram[a,b]

We enrolled and consented 379 patients (46% participation, Figure 1), 278 of whom had analyzable data (Figure 1). Over 75% (n=209) of patients completed at least one post-baseline survey. Patients who did not participate were significantly older (p<0.001) and less likely to have breast cancer (p=0.04) than participants, although there were no gender differences.

Patients with analyzable data were significantly more likely to be married (p=0.002) and have higher incomes (p=0.03) than those with non-analyzable data; no other demographic differences were significant. Neither baseline clinician (Table 1) nor patient characteristics (Table 2) demonstrated significant differences between arms.

TABLE 1. Baseline Characteristics of the Clinician Population[a,b,c]

	Intervention n=48 (20 clusters)	**Control n=43 (21 clusters)**
Female sex – no. (%)	30 (63)	22 (51)
Discipline – no. (%)		
MD	36 (75)	30 (70)
NP	11 (23)	11 (26)
PA	1 (2.1)	2 (4.7)
Cluster size – mean (95% CI)	3.3 (2.9-3.8)	2.8 (2.3-3.2)
Years of practice – mean (95% CI)	12.8 (9.7-16.0)	10.2 (7.4-12.9)
Disease center[d] – no. (%)		
Breast oncology		
Gastrointestinal, Genitourinary, Head & Neck, Neurology,	11 (23)	10 (23)
Sarcoma, Thoracic, other	27 (56)	22 (51)
Hematologic Malignancies, Lymphoma	6 (13)	6 (14)
Community-based clinics	4 (8.3)	5 (11.6)
Percentage of screened panel patients identified as eligible by surprise question – mean (95% CI)	23 (16-30)	27 (19-36)

[a] P values between arms are all > 0.07
[b]Percentages may not sum to exactly 100 due to rounding.
[c]13% are missing years of practice, 2% missing pts eligible by surprise and all else have no missings.
Calculations for percentages were based on non-missing data.
[d]Disease center does not include gynecologic oncology due to a concurrent trial being conducted at that center

Intervention Measures

We trained 47 of 48 intervention clinicians, and clinicians rated the training as effective (4.3/5, SD=0.7). Of those trained, 83% (n=39) received at least one reminder to conduct a serious illness conversation, and of those reminded, 87% (n=34) completed at least one conversation. Clinicians reported a median conversation duration of 19 minutes (range 5-70).

TABLE 2. Baseline Characteristics of the Patient Population[a,b,c]

	Intervention n=134	**Control n=144**
Age in years - mean (95% CI)	62 (58-65)	62 (58-66)
Female sex – no. (%)	72 (54)	76 (53)
Race[d] – no. (%)		
White	124 (93)	127 (93)
Black or African American	2 (1.5)	3 (2.2)
Other	7 (5.3)	7 (5.1)
Hispanic – no. (%)	3 (2.3)	4 (2.9)
Married/partnered – no. (%)	107 (80)	115 (80)
Income ≥$75,000 – no. (%)	77 (60)	65 (50)
Disease center [e] – no. (%)		
Breast oncology		
Gastrointestinal, Genitourinary, Head & Neck, Neurology,	32 (24)	37 (26)
Sarcoma, Thoracic, other	93 (69)	91 (63)
Hematologic Malignancies, Lymphoma	9 (6.7)	16 (11.1)
Health insurance type – no. (%)		
Medicare	65 (49)	60 (43)
Medicaid/Mass Health	9 (6.8)	11 (8.0)
Private	58 (44)	65 (47)
No insurance	0	1 (0.7)
Other	0	1 (0.7)
Patient-reported health status – no. (%)		
Relatively healthy and not seriously ill	21 (16)	24 (17)
Relatively healthy and terminally ill	77 (58)	73 (53)
Seriously but not terminally ill	26 (20)	28 (20)
Seriously and terminally ill	9 (6.8)	14 (10.1)
College, graduate or professional school – no. (%)	112 (84)	112 (80)[a]

P values between arms are all >0.21.

[b] Percentages will not sum to exactly 100 due to rounding.

[c] Since the percent missing for any variable was less than 7%, missing data are not shown in this table. Calculations for percentages were based on non-missing data.

[d] Race or ethnic group was self-reported.

[e] Disease center does not include gynecologic oncology due to a concurrent trial being conducted at that center.

Patient Measures for Decedents

Goal-Concordant Care

We matched a Family Perception[28] survey to an appropriately-timed Life Priorities[28] survey for 64 decedents (38 intervention, 26 control). There was no significant difference in the median number of top-three goals met between study arms (Table 3).

Peacefulness

There were no significant differences between study arms for decedents in the PEACE[35] subscales at baseline or within three months before death (Table 3).

Patient Measures for Total Population

Therapeutic Alliance

Among all patients, mean scores of the Human Connection Scale[36] did not differ significantly between arms at baseline (25.3 (CI 24.8-25.8) intervention vs. 25.5 (CI 25.0-26.0) control, p=0.60)), at 14 weeks after baseline (25.5 (CI 24.8-26.2) intervention vs. 25.7 (CI (25.1-26.2) control, p=0.65), or at 24 weeks after baseline (25.5 (CI 25.0-26.1) intervention and 25.4 (CI 24.8-26.0) vs. control, p=0.71) (Figure 2).

Anxiety

Among all patients, the proportion of patients reporting moderate or severe anxiety symptoms did not differ significantly between arms at baseline (9.6% control vs. 9.0% intervention (p=0.85)). At 14 weeks after baseline, the proportion of patients reporting moderate or severe anxiety symptoms was significantly lower in the intervention arm (10% vs. 5%, p=0.05). At 24 weeks after baseline, intervention patients remained less likely than control patients to report moderate or severe anxiety symptoms (10.4% vs. 4.2%, p=0.02) (Figure 2).

Depression

Among all patients, the proportion of patients reporting moderate or severe depression symptoms did not differ significantly between arms at baseline (20% control vs. 19% intervention (p=0.84). At 14 weeks after baseline, the proportion of patients reporting moderate or severe depression symptoms was significantly lower in the intervention arm (21% vs. 11%, p=0.04). At 24 weeks after baseline, the proportion of patients reporting moderate or severe depression symptoms did not differ significantly between arms (18% vs. 13%, p=0.31) (Figure 2).

Survival

Median 2-year survival did not differ between study arms (13.9 months intervention, 13.6 months control, log-rank p=0.91).

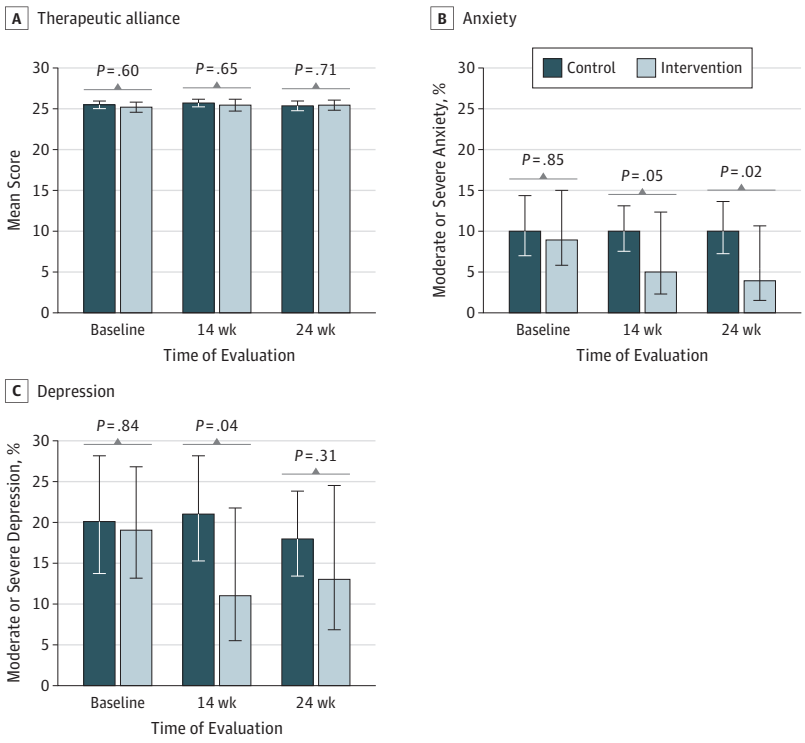

FIGURE 2: Outcomes of Assessments of Anxiety, Depression and Therapeutic Alliance

DISCUSSION

The results of this cluster-randomized controlled trial of a communication quality-improvement intervention were null with respect to the co-primary outcomes of goal-concordant care and peacefulness at the end of life and the secondary outcome of therapeutic alliance. However, the trial demonstrated a significant improvement in depression symptoms and a significant and sustained improvement in anxiety symptoms in intervention patients. Survival did not differ between arms.

Several explanations for the lack of impact of our intervention on the primary outcomes are possible. First, because of smaller number of expected deaths and poor survey response, our study was under-powered. Second, because of the absence of a strong patient-centered measure of goal-concordant care, we used an unvalidated survey. Third, our measurements of goal-concordant care were dependent on patient responses late in the illness and family responses early in bereavement, which may have been too burdensome.[43] Fourth, although

we measured peacefulness with a validated scale,[35] this measure may have been inadequate to capture elements of peacefulness that respond to improved communication. As a result, we are uncertain whether our intervention was ineffective at improving these outcomes, if our outcome measures were not appropriate or feasible, or if we lacked sufficient numbers to detect meaningful differences. Our challenges reflect the urgent need in our field for patient-centered measures of communication that are agreed upon, validated, and demonstrably sensitive to communication interventions.[44-48]

This trial demonstrated significant improvements in the secondary outcomes of moderate-to-severe anxiety and depression symptoms that regularly burden patients with cancer.[49-51] In contrast to prior research,[24,25,52] this study, using well-validated and widely-used measures, demonstrated significantly decreased rates of anxiety and depression symptoms within two weeks of the conversation in the intervention group, and the reduction in anxiety symptoms lasted until at least 24 weeks after baseline, suggesting that trained oncologists can discuss important and difficult topics without causing harm and with potential benefit. To our knowledge, this is the first study to identify a clinically meaningful benefit to psychological symptoms from a structured communication approach, suggesting that psychological outcomes be considered primary outcomes in future communication studies in oncology. This finding also highlights the need for measurement of communication and outcomes over the illness trajectory, not just at the end of life, which may help to better understand how to improve patients' well-being as they live with serious illness.

We found that intervention clinicians readily adopted the program; they attended the training and rated it as effective. They conducted serious illness conversations in a feasible timeframe with respect to the constraints of a typical oncology practice. We expect these findings to be transferrable to other clinical contexts that treat advanced cancer patients while also recognizing that these intervention components require substantial organizational resources.

Among several study limitations was insufficient power for the primary outcomes. Our patient participation rate in the trial, while low, is consistent with other population-level trials of seriously ill patients.[43,53] Due to lower patient accrual rates, fewer deaths than expected, longitudinal design, and difficulties obtaining surveys from patients and bereaved caregivers, a relatively large number of patients were not included in the primary outcomes analysis. However, nonparticipants and unanalyzed participants were not meaningfully different from analyzed participants, and randomization still produced comparable groups between study arms. The variation in timing of outcome assessment may also be a limitation; however, we found that dropout and timing of measurement were similar across arms. Use of the surprise question by all clinicians and frequent survey completion by all patients may have prompted conversations in the control arm, attenuating potential between-arm differences. Additionally,

findings may not be generalizable because the study was conducted at a single oncology institution with a fairly small number of participants that were relatively white, college-educated, and affluent. Finally, the multi-component nature of the intervention prevents assessment of which components contributed to the outcomes.

The results of this cluster-randomized trial were null with respect to the co-primary outcomes of goal-concordant care and peacefulness for decedents (but were significantly under-powered for the primary outcomes) but demonstrated significant reductions in the secondary outcomes of anxiety and depression symptoms immediately after the conversation and a sustained reduction in anxiety among intervention patients in the total population. This study showed that a feasible system-level communication intervention with high clinician adoption may improve some meaningful patient outcomes among advanced cancer patients. Advancements in serious illness communication interventions will require more reliable and well-accepted patient-centered outcome measures and additional testing of the impact on patients throughout their illness trajectory.

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NEDERLANDSE SAMENVATTING

Het doel van dit proefschrift was om de impact van longkanker beter in kaart te brengen en te onderzoeken hoe we vroegtijdige palliatieve en ondersteunende zorg voor deze patiënten beter kunnen vormgeven. Dit werd gedaan door een combinatie van kwantitatief en kwalitatief onderzoek. Daarbij is het ook van belang aan te geven dat een deel van deze studies werd verricht in een bredere patiëntenpopulatie waarin patiënten met ongeneeslijke kanker geïncludeerd werden. Het primaire doel van dit proefschrift was echter wel om de bevindingen specifiek voor patiënten met longkanker verder uit te lichten. In dit hoofdstuk beschrijven wij, in begrijpelijk Nederlands, de belangrijkste bevindingen uit dit proefschrift gecombineerd met de conclusies en implicaties voor de huidige klinische praktijk.

Palliatieve zorg voor patiënten met longkanker

In **hoofdstuk 2** beschreven wij een systematische review waarin de effecten van gezamenlijke besluitvorming voor patiënten met longkanker werd onderzocht. Dit proces vormt een integraal onderdeel van de oncologische zorg maar de effecten hiervan zijn nog niet eerder duidelijk in kaart gebracht. Wij kozen ervoor om ons te richten op de effecten op angst, depressie en zorggebruik. In de literatuur vonden wij 13 publicaties die in het onderzoek werden geïncludeerd. Deze publicaties lieten zien dat wanneer patiënten en artsen gebruik maken van gezamenlijke besluitvorming dit angst, depressie en zorggebruik onder patiënten kan verminderen. Gezamenlijke besluitvorming lijkt daarom dus een belangrijk en centraal onderdeel te moeten zijn van de zorg voor patiënten met longkanker.

In **hoofdstuk 3** presenteerden wij vervolgens de uitkomsten van een gerandomiseerde trial waarin de effecten van vroegtijdige en structurele palliatieve zorg voor patiënten met longkanker werd onderzocht. In totaal werden 223 patiënten met longkanker die een vorm van systeemtherapie ondergingen geïncludeerd. Patiënten gerandomiseerd tot de interventiegroep vulden op vaste tijdstippen de Lastmeter in en hadden een aanvullend gesprek met een psychosociaal verpleegkundige waarin de uitslag van de Lastmeter werd besproken. Vanuit hier werden deze patiënten ook verder verwezen naar andere paramedici (e.g. een psycholoog) als hier behoefte aan was. Patiënten werden in totaal voor 25 weken vervolgd. Wij kozen ervoor om de effecten op kwaliteit van leven, angst, depressie, patiënttevredenheid, zorggebruik nabij overlijden en overleving te meten. De uitkomsten van dit onderzoek lieten geen belangrijke verschillen zien tussen beide studiegroepen ten aanzien van kwaliteit van leven, angst, depressie, patiënttevredenheid of overleving. Wel vonden wij belangrijke verschillen in zorggebruik nabij het overlijden waarbij patiënten in de interventiegroep minder agressieve zorg (e.g. minder chemotherapie) ontvingen in de laatste maanden van hun leven.

In **hoofdstuk 4** werd vervolgens de prognostische waarde van de Lastmeter score onderzocht. Alle patiënten die gerandomiseerd waren tot de interventiegroep werden geïncludeerd in deze studie. Hierna werden vijf relevante prognostische variabelen gekozen en toegevoegd aan een multivariabel predictiemodel om de eenjaarsoverleving van patiënten met longkanker te voorspellen. Nadat de Lastmeter-score werd toegevoegd aan dit model verbeterde zowel de voorspellende als de onderscheidende waarde. Hiernaast bleek uit dit onderzoek dat patiënten met een hoge Lastmeter-score (>4) een lagere kwaliteit van leven ervaarden met daarbij meer angst en depressie. Ook leefden patiënten met een hoge Lastmeter-score significant korter dan patiënten met een lage score. Hierbij is het belangrijk aan te geven dat deze verschillen niet verklaard konden worden vanuit verschillen in socio-demografische of klinische variabelen.

Gesprekken tussen oncologen en patiënten met kanker

In de komende hoofdstukken wordt de focus uitgebreid naar alle patiënten met ongeneeslijke kanker. Gesprekken tussen oncologen en hun patiënten staan centraal in de zorg voor deze patiëntenpopulatie. In **hoofdstuk 5** werd een kwalitatieve studie gepresenteerd waarin 25 van dit soort gesprekken nader wordt geanalyseerd Alle oncologen die geïncludeerd werden in deze studie waren getraind in het gebruik van de "Serious Illness Conversation Guide". Deze gesprekstool legt de basis voor oncologen om met patiënten in gesprek te gaan over hun persoonlijke doelen, wensen en voorkeuren voor het levenseinde. Uit deze data werden vijf belangrijke thema's gedistilleerd. Patiënten en hun oncologen spraken open over het levenseinde en patiënten gaven hierin vaak expliciet hun wensen rondom het levenseinde aan zonder dat de oncoloog hier direct naar vroeg. Wel bleek dat oncologen moeite hadden om in dieper in te gaan op emotionele uitingen of ambivalente uitspraken van patiënten. Daarnaast werd vaak onduidelijk gesproken over de prognose van patiënten, zelfs als zij hier direct naar vroegen. We concluderen dat oncologen zich hier bewuster van dienen te worden maar ook voldoende handvaten moeten krijgen om dit soort gesprekken tijdig te voeren.

In **hoofdstuk 6** analyseerden wij de documentatie over deze gesprekken. We vergeleken de audio-opnames van de gesprekken met de documentatie van de oncoloog. Hierbij werd de congruentie tussen deze opnames en de documentatie gescoord. Dit werd gedaan aan de hand van een aantal specifieke domeinen. Gesprekken gevoerd door de oncoloog konden gedocumenteerd worden als vrije tekst (naar invulling van de oncoloog) of samengevat worden binnen een bestaand template waarin alle domeinen structureel aan bod kwamen. De resultaten van dit onderzoek laten zien dat belangrijke informatie over prognose niet of verkeerd wordt gedocumenteerd wanneer oncologen deze gesprekken als vrije tekst documenteren. Documentatie van gesprekken over het levenseinde zou daarom gedaan moeten worden

in een uniform template waarin alle belangrijke aspecten van deze zorg naar voren komen. De gerandomiseerde trial waar de data van deze twee hoofdstukken uit afkomstig zijn werd beschreven in **Appendix I.**

Overlevers van longkanker

Het aantal overlevers van longkanker is in de afgelopen jaren sterk gegroeid door screening en nieuwe behandelmodaliteiten. De complexiteit van de zorg voor deze patiëntenpopulatie is daarmee ook toegenomen. In **hoofdstuk 7** gingen wij dieper in op de parallellen tussen de zorg voor overlevers van kanker en de palliatieve zorg. Wij concluderen hierbij dat er een grote overlap bestaat tussen deze twee zorgdomeinen. Deze overlap komt met name naar voren door een aantal belangrijke overeenkomsten: 1) verwarring over de terminologie binnen beide zorgdomeinen; 2) het feit dat de zorg binnen beide domeinen per definitie multidisciplinair is waardoor er meerdere specialisten betrokken zijn; 3) het gebrek aan consensus binnen beide zorgdomeinen over het optimale model om deze zorg te leveren; 4) de toegenomen vraag naar dit type zorg; 5) de toedracht van de zorg die geleverd wordt (e.g. symptoombestrijding, verlichting van emotionele klachten); en 6) de noodzaak om betere kwaliteitsparameters te ontwikkelen en definiëren waardoor de kwaliteit van deze zorg geoptimaliseerd kan worden.

In **hoofdstuk 8** beschreven wij vervolgens de ontwikkeling van een generiek meetinstrument om de belangrijkste gezondheid gerelateerde problemen van overlevers van kanker tijdig en structureel in kaart te brengen. Drie expert-panels op het gebied van longkanker, borstkanker en colorectaal kanker werden samengesteld. Elk van deze panels bestond uit ervaringsdeskundigen (e.g. patiënten), medische professionals (e.g. artsen), en paramedici (e.g. psychologen). Het "International Classification of Functioning, Disability, and Health" werd gebruikt als basis voor dit meetinstrument. In totaal werden er 101 experts geïncludeerd in de Delphi studie. Gedurende twee rondes selecteerden deze experts onafhankelijk van elkaar de meest relevante en meest voorkomende problemen waar overlevers van kanker mee te maken krijgen. De geselecteerde categorieën werden vervolgens gevalideerd door ze te vergelijken met items van drie verschillende vragenlijsten samengesteld voor overlevers van kanker. Dit resulteerde in de basis voor de "Cancer Survivor Core Set" bestaande uit 19 gevalideerde categorieën die relevant zijn voor overlevers van kanker. Verdere validatie en optimalisatie van dit meetinstrument is noodzakelijk voordat deze in de klinische praktijk kan worden gebruikt.

Algemene conclusies en aanbevelingen

Vroegtijdige palliatieve en ondersteunende zorg voor patiënten met longkanker is van belang om te komen tot passende zorg rondom (en voorafgaand aan) het levenseinde. Eerdere studies hebben een duidelijk positief effect laten zien wanneer dit soort zorg vroegtijdig wordt ingezet. Daarnaast vormt gezamenlijke besluitvorming een essentieel onderdeel hiervan waarbij de

ontwikkeling van keuzehulpen ("decision aids") artsen een handvat kan bieden om patiënten en hun naasten te helpen tot een juist besluit te komen. Daarnaast kunnen de patiënten met longkanker die het risico lopen om binnen een jaar te overlijden beter in kaart worden gebracht door het gebruikt van de Lastmeter-score of een vergelijkbare vragenlijst. De combinatie van deze score met de "surprise question" (Zou het mij verbazen als deze patiënt over een jaar overleden zou zijn?) kan hierbij een belangrijke overweging zijn.

Het tijdig voeren van open gesprekken over het levenseinde met patiënten die longkanker hebben is een ander belangrijk element om te zorgen dat deze patiënten passende zorg krijgen. Artsen dienen beter getraind te worden in dit soort gespreksvorming. Daarnaast is het van belang dat deze gesprekken adequaat en gecentraliseerd gedocumenteerd worden zodat meerdere zorgverleners – alsmede de patiënt – hier toegang tot hebben. Idealiter zou dit een "dynamisch" document zijn dat aan verandering onderhevig is gedurende het ziektebeloop.

Ook de zorg voor overlevers van (long)kanker kan verder geoptimaliseerd worden. Met name door alle nieuwe behandelmodaliteiten voor longkanker (e.g. immuuntherapie) zal deze ziekte in de komende jaren mogelijk een chronische ziekte worden. Juist daarom is het van belang overlevers van longkanker tijdelijk te screenen en in de eerste jaren na hun diagnose structureel te vervolgen. De huisarts speelt hierin een uitermate belangrijke rol.

Een aantal aanbevelingen voor de toekomst zijn van belang in het kader van dit proefschrift. Waarschijnlijk zijn er meer studies nodig om het belang en effect van vroegtijdige palliatieve zorg nog beter in kaart te brengen. Idealiter zouden dit grotere (inter)nationale studies zijn waarin een vergelijkbaar model om palliatieve zorg in te bedden wordt gebruikt. Juist dan is het mogelijk om structureel de effecten van tijdige implementatie te onderzoeken. Hierbij dient ook consensus te bestaan over de beste uitkomstmaten om de kwaliteit van deze zorg te meten. Ook de rol van naasten zou hierin meegenomen moeten worden.

Daarnaast is de rol van palliatieve zorg nu met name gericht op de oncologische zorg. Uitbreiding van deze zorg naar andere domeinen (e.g. de zorg voor patiënten met ernstig COPD) is een belangrijke ontwikkeling voor de nabije toekomst. Uiteindelijk zal de rol van palliatieve en ondersteunende zorg voor patiënten met longkanker verder gaan groeien in de komende jaren. Juist daarom dient er ook vroegtijdig in de opleiding tot arts structureel aandacht voor dit zorgdomein te zijn om daadwerkelijk de juiste zorg te leveren waarin de patiënt echt centraal staat.

DANKWOORD

Hoe vreemd dit ook mag lijken, het dankwoord is toch echt het meest gelezen hoofdstuk van een proefschrift. Ook hier mag dit geheel dus zeker niet ontbreken. Graag wil ik een aantal mensen in het bijzonder bedanken. Zonder hen was dit proefschrift niet tot stand gekomen.

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Daarnaast wil ik ook mijn viertallige promotieteam bestaande uit twee longartsen en twee huisartsen bedanken. Te beginnen met Prof. dr. H.A.M. Kerstjens, beste **Huib**. Wat een geluk heb ik gehad met jou als eerste promotor. Jouw uiterst heldere denktrant en kritische (weder) vragen hebben dit proefschrift tot een hoger niveau gebracht. Daarnaast was er vanuit jou altijd ruimte en interesse voor de mens achter de promovendus. Die extra aandacht - juist op de momenten waarin de combinatie van gelijktijdig promoveren en coschappen lopen zwaarder was – heb ik als bijzonder fijn en ondersteunend ervaren. Dank!

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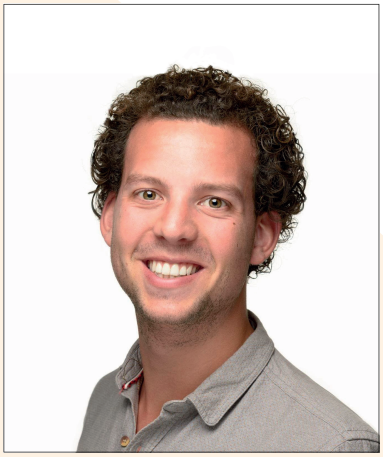

Curriculum Vitae

Olaf Geerse was born on August 15, 1991 in Zoetermeer, the Netherlands. In 2009, he graduated from secondary school at Erasmus College in Zoetermeer. From 2009 to 2010, Olaf studied Biology at the University of Leiden where he obtained his propaedeutic diploma. He subsequently studied at the University of Groningen from 2010 to 2013 and obtained his International Bachelor of Medicine with Honours. Thereafter, Olaf got accepted to participate in a five-year MD-PhD program (2013 – 2019) during which he combined his Master of Medicine with a PhD. He successfully completed his thesis at the Department of Pulmonary Diseases and Tuberculosis and the Department of General Practice within the University Medical Center Groningen. Throughout his PhD, he worked closely with Prof. dr. H.A.M. Kerstjens, Prof. dr. M.Y. Berger, Dr. T.J.N. Hiltermann and Dr. A.J. Berendsen. As part of this program, Olaf also spent a year as a research fellow working with the Serious Illness Care Program at the Harvard T.H. Chan School of Public Health in Boston. Further, Olaf became a student board member of the Royal Dutch Medical Association and participated in the Master Honours Programme. He also worked as an academic tutor during his MD-PhD and is participating in the Journal of Oncology Practice mentoring program. Currently, Olaf works as a resident in Pulmonary Medicine at the Onze Lieve Vrouwe Gasthuis (OLVG) Hospital in Amsterdam, the Netherlands. In the future, he aims to combine his clinical work as a pulmonary oncologist with educational activities as well as research in the field of palliative and survivorship care.

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