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Early palliative care for adults with advanced cancer (Review)

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[Intervention Review]

Early palliative care for adults with advanced cancer

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ABSTRACT

Background

Incurable cancer, which often constitutes an enormous challenge for patients, their families, and medical professionals, profoundly affects the patient's physical and psychosocial well-being. In standard cancer care, palliative measures generally are initiated when it is evident that disease-modifying treatments have been unsuccessful, no treatments can be offered, or death is anticipated. In contrast, early palliative care is initiated much earlier in the disease trajectory and closer to the diagnosis of incurable cancer.

Objectives

To compare effects of early palliative care interventions versus treatment as usual/standard cancer care on health-related quality of life, depression, symptom intensity, and survival among adults with a diagnosis of advanced cancer.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, OpenGrey (a database for grey literature), and three clinical trial registers to October 2016. We checked reference lists, searched citations, and contacted study authors to identify additional studies.

Selection criteria

Randomised controlled trials (RCTs) and cluster-randomised controlled trials (cRCTs) on professional palliative care services that provided or co-ordinated comprehensive care for adults at early advanced stages of cancer.

Data collection and analysis

We used standard methodological procedures as expected by Cochrane. We assessed risk of bias, extracted data, and collected information on adverse events. For quantitative synthesis, we combined respective results on our primary outcomes of health-related quality of life, survival (death hazard ratio), depression, and symptom intensity across studies in meta-analyses using an inverse variance random-effects model. We expressed pooled effects as standardised mean differences (SMDs, or Hedges' adjusted *g*). We assessed certainty of evidence at the outcome level using GRADE (Grading of Recommendations Assessment, Development, and Evaluation) and created a 'Summary of findings' table.

Main results

We included seven randomised and cluster-randomised controlled trials that together recruited 1614 participants. Four studies evaluated interventions delivered by specialised palliative care teams, and the remaining studies assessed models of co-ordinated care. Overall, risk of bias at the study level was mostly low, apart from possible selection bias in three studies and attrition bias in one study, along with insufficient information on blinding of participants and outcome assessment in six studies.

Compared with usual/standard cancer care alone, early palliative care significantly improved health-related quality of life at a small effect size (SMD 0.27, 95% confidence interval (CI) 0.15 to 0.38; participants analysed at post treatment = 1028; evidence of low certainty). As re-expressed in natural units (absolute change in Functional Assessment of Cancer Therapy-General (FACT-G) score), health-related quality of life scores increased on average by 4.59 (95% CI 2.55 to 6.46) points more among participants given early palliative care than among control participants. Data on survival, available from four studies enrolling a total of 800 participants, did not indicate differences in efficacy (death hazard ratio 0.85, 95% CI 0.56 to 1.28; evidence of very low certainty). Levels of depressive symptoms among those receiving early palliative care did not differ significantly from levels among those receiving usual/standard cancer care (five studies; SMD -0.11, 95% CI -0.26 to 0.03; participants analysed at post treatment = 762; evidence of very low certainty). Results from seven studies that analysed 1054 participants post treatment suggest a small effect for significantly lower symptom intensity in early palliative care compared with the control condition (SMD -0.23, 95% CI -0.35 to -0.10; evidence of low certainty). The type of model used to provide early palliative care did not affect study results. One RCT reported potential adverse events of early palliative care, such as a higher percentage of participants with severe scores for pain and poor appetite; the remaining six studies did not report adverse events in study publications. For these six studies, principal investigators stated upon request that they had not observed any adverse events.

Authors' conclusions

This systematic review of a small number of trials indicates that early palliative care interventions may have more beneficial effects on quality of life and symptom intensity among patients with advanced cancer than among those given usual/standard cancer care alone. Although we found only small effect sizes, these may be clinically relevant at an advanced disease stage with limited prognosis, at which time further decline in quality of life is very common. At this point, effects on mortality and depression are uncertain. We have to interpret current results with caution owing to very low to low certainty of current evidence and between-study differences regarding participant populations, interventions, and methods. Additional research now under way will present a clearer picture of the effect and specific indication of early palliative care. Upcoming results from several ongoing studies (N = 20) and studies awaiting assessment (N = 10) may increase the certainty of study results and may lead to improved decision making. In perspective, early palliative care is a newly emerging field, and well-conducted studies are needed to explicitly describe the components of early palliative care and control treatments, after blinding of participants and outcome assessors, and to report on possible adverse events.

PLAIN LANGUAGE SUMMARY

Early palliative care for adults with advanced cancer

Review question

What is the evidence for the effects of early palliative care on quality of life, survival, depression, and symptom intensity in people with advanced cancer?

Background

Frequently, cancer is diagnosed at a late stage, and the disease might have progressed through anticancer treatment. Patients can choose to start or continue anticancer treatment at the potential cost of side effects. Standard care means that all patients are offered palliative care towards the end of life. However, patients may be able to receive palliative care a lot earlier. This approach, which is known as early palliative care, begins at the time of, or shortly after, the diagnosis of advanced cancer. Often, early palliative care is combined with anticancer treatment such as chemotherapy or radiotherapy. Early palliative care, whether provided by the attending oncologist or by specialist teams, involves empathetic communication with patients about their prognosis, advance care planning, and symptom assessment and control.

Study characteristics

In October 2016, we searched for clinical trials on early palliative care in adults with advanced cancer. We included seven studies and found 20 ongoing studies. Most of the studies included participants older than 65 years of age on average, diagnosed with different tumour types and receiving treatment in tertiary care centres in North America. Most of these studies compared early palliative care with standard oncological (cancer) care. All studies were funded by government agencies.

Key results

When evaluated together in a meta-analysis, studies showed that in patients with advanced cancer, early palliative care may slightly increase quality of life. It may also decrease symptom intensity to a small degree. Effects on survival and depression are uncertain. A single

study reported side effects (adverse events), for example, more pain and reduced appetite. For the remaining six studies, information about side effects was not published, but trial authors told us they had not observed any.

Certainty of the evidence

We rated the certainty of the evidence using four levels: very low, low, moderate, and high. Evidence of very low certainty means that we have little confidence in the results. Evidence of high certainty means that we are very confident in the results. We found that certainty of the evidence was low for health-related quality of life and symptom intensity, and was very low for depression and survival. We downgraded certainty of the evidence for various reasons, for example, problems in the way studies were carried out, differences between studies, and the small number of studies. We remain uncertain about the effects of early palliative care; therefore we have to interpret the results with caution. When published, ongoing studies may provide more evidence, and this may affect the certainty of the results.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Early palliative care for adults with advanced cancer

Clinical question: Should early palliative care be preferred over treatment as usual for improving health-related quality of life, depression, and symptom intensity in patients with advanced cancer?

Patient or population: patients with advanced cancer

Settings: mainly outpatient care in Australia, Canada, Italy, and the USA
Intervention: early palliative care

Comparison: treatment as usual

Follow-up: at 12 weeks or mean difference in repeated measurement results for longitudinal designs

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with treatment as usual	Risk with early palliative care				
Health-related quality of life (HRQOL), SD units: measured on FACIT-Pal, TOI of FACT-Hep, TOI of FACT-L, FACT-G, McGill Quality of Life, FACIT-Sp. Higher scores indicate better HRQOL. Follow-up: range 12 weeks to 52 weeks	HRQOL score improved on average **0.27 (95% CI 0.15 to 0.38) SDs** more in early palliative care participants than in control participants		-	1028 (7 RCTs)	⊕⊕⊖⊖ LOW[1,2,3]	By conventional criteria, an SMD of 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect (Cohen 1988)
Health-related quality of life (HRQOL), natural units: measured on FACT-G (from 0 to 108)	Baseline control group mean score at 70.5 points[a]	HRQOL score improved on average **4.59 (95% CI 2.55 to 6.46) points** more in early palliative care participants than in control participants	-	1028 (7 RCTs)	⊕⊕⊖⊖ LOW[1,2,3]	Calculated by transforming all scales to the FACT-G in which the minimal clinically important difference is approximately 5 and the SD in the cancer validation sample was 17.0 (Brucker 2005)
Survival: estimated with the unadjusted death hazard ratio	Study population[b]		HR 0.85, 95% CI 0.56 to 1.28	800 (4 RCTs)	⊕⊖⊖⊖ VERY LOW[1,4,5,6]	
	61 per 100	**56 per 100 (41-71)**				

Depression, SD units: measured on CES-D, HADS-D, PHQ-9. Higher scores indicate higher depressive symptom load. Follow-up: range 12 weeks to 52 weeks	Depression score improved on average **-0.11 (95% CI -0.26 to 0.03) SDs** more in early palliative care participants than in control participants		-	762 (5 RCTs)	⊕⊖⊖⊖ VERY LOW[1,2,4]	By conventional criteria, an SMD of 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect (Cohen 1988)
Depression, natural units: measured on CES-D (from 0 to 60). Higher scores indicate higher depressive symptom load	Baseline control group mean score at 13.8 points[c]	Depressive symptoms score improved on average **-0.98 (95% CI -2.31 to 0.27) points** more in early palliative care participants than in control participants	-	762 (5 RCTs)	⊕⊖⊖⊖ VERY LOW[1,2,4]	Calculated by transforming all scales to CES-D and applying an SD of 8.9 from baseline control group score in Bakitas 2009
Symptom intensity, SD units: measured on ESAS, QUAL-E Symptom Impact Subscale, SDS, RSC, LCS of FACT-L, HCS of FACT-Hep. Higher scores indicate higher symptom intensity. Follow-up: range 12 weeks to 52 weeks	Symptom intensity score improved on average **-0.23 (95% CI -0.35 to -0.1) SDs** more in early palliative care participants than in control participants		-	1054 (7 RCTs)	⊕⊕⊖⊖ LOW[1,2,3]	By conventional criteria, an SMD of 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 a large effect (Cohen 1988)
Symptom intensity, natural units: measured on ESAS (from 0 to 900). Follow-up: range 12 weeks to 52 weeks	Baseline control group mean score at 286.3 points[c]	Symptom intensity symptoms score improved on average **-35.4 (95% CI -53.9 to -15.4) points** more in early palliative care participants than in control participants	-	1054 (7 RCTs)	⊕⊕⊖⊖ LOW[1,2,3]	Calculated by transforming all scales to the ESAS and applying an SD of 154.0 from baseline control group score in Bakitas 2009
Adverse events	See comment	See comment	Not estimable	1614 (7 RCTs)	See comment	Most often, study authors did not address assessment or findings on adverse events in their study publications. However, on request, authors of 6 studies described the tolerability of early palliative care as very good. A single study mentioned adverse events only in the early palliative care group, i.e. higher percentage of participants with severe scores for pain and poor appetite along with

higher level of unmet needs (Tatter-sall 2014)

*__Risk in the intervention group__ (and its 95% confidence interval) is based on assumed risk in the comparison group and __relative effect__ of the intervention (and its 95% CI)

[a]Approximate average of baseline control group FACT-G scores across 4 included studies (Bakitas 2009; Bakitas 2015; Maltoni 2016; Temel 2010)

[b]12-Month follow-up control group risk in the largest study reporting on survival (Bakitas 2009)

[c]Baseline control group CES-D score in the largest study reporting on depression (Bakitas 2009)

CI: confidence interval; GRADE: Grading of Recommendations Assessment; HR: unadjusted death hazard ratio; SD: standard deviation; SMD: standardised mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1]We downgraded 2 points owing to very serious limitations in study quality (high risk of bias across studies)
[2]We decided against downgrading for indirectness, although 2 studies were conducted exclusively in patients with metastatic pancreatic and advanced lung cancer, respectively (Maltoni 2016; Temel 2010). We decided against downgrading for inconsistency, as we did not detect significant heterogeneity
[3]We decided against downgrading for imprecision, as the optimal information size (OIS) criterion was met, and the 95% confidence interval around the difference in effect between intervention and control excludes zero
[4]We downgraded 1 point for imprecision, as the optimal information size (OIS) criterion was met, but the 95% confidence interval around the difference in effect between intervention and control includes zero. The 95% confidence interval fails to exclude harm
[5]We decided against downgrading for important inconsistency (large I^2) because we had downgraded by 3 points already
[6]We decided against downgrading for indirectness, as only a single study was conducted exclusively in patients with advanced lung cancer (Temel 2010)

BACKGROUND

Research has led to remarkable improvements in cancer treatment, but at the time of diagnosis, some patients still have a reduced life expectancy. Incurable cancer can pose an enormous challenge for patients, their families, and medical professionals, and can affect patients' quality of life in many ways (Addington-Hall 1995). Interventions tailored to improve the physical and psychological well-being of people with cancer are of utmost importance. Palliative care comprises an "approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" (WHO 2013). Interdisciplinary care and caregiver support assist healthcare professionals in delivering the essential elements of palliative care by managing the patient's quality of life and controlling symptoms (Hui 2013a). However, although early access is inherent in the definition of palliative care, usual practice is still limited to the terminal phase of illness.

Description of the condition

With an incident rate of 14.9 million cases and 8.2 million deaths in 2013, malignant neoplastic diseases remain one of the leading causes of death worldwide (Global Burden of Disease Cancer Collaboration 2015). Globally, the most common entities and causes of cancer-related mortality, measured as disability-adjusted life-years (DALYs), are breast cancer in women and lung cancer in men. Cancer incidence has been estimated to increase yearly by 1%, with the growing population worldwide and the demographic shift towards an ageing population in developed countries serving as the paramount factors for future cancer burden (Boyle 2008).

Despite significant progress in our understanding of the risk factors for cancer, development of methods for early identification of some cancers or precancerous diseases, and sound advances in the treatment of many cancers previously deemed fatal (e.g. breast, prostate, melanoma, Hodgkin's disease), cancer continues to cause the premature death of many individuals (particularly cancers of the pancreas, lung, brain, and stomach) (Prigerson 2015; Quaresma 2015). At the time of diagnosis, chances of curative treatment are often minimal owing to advanced disease. The American Cancer Society defines advanced cancer as "cancers that cannot be cured", and metastatic cancer as tumours that "have usually spread from where they started to other parts of the body" (American Cancer Society 2013). However, not all advanced cancers are metastatic. For example, brain tumours may be considered advanced because they are not curable, and life-threatening, even in the absence of metastasis. In addition, the survival rate of patients remains very poor, especially for metastatic lung cancer and for pancreatic and biliary tract malignancies.

Because death is anticipated in many of these cases, it is essential that appropriate treatment plans are developed to improve survival, while aiming for a subjectively worthwhile quality of life. Both symptom control and disease-modifying therapy are needed in these situations. By causing a major decline in physical efficiency and persistent chronic pain, advanced cancer regularly puts the physical and psychological integrity of patients at high risk. In many cases, appropriate execution of necessary medical treatments and of the daily routine at home demands continuous familial and often additional external support. Symptoms such as pain, fatigue/drowsiness, low appetite and/or anorexia-cachexia syndrome, dysphagia, nausea, diarrhoea, constipation, shortness of breath, and mental confusion are often independent prognostic factors for predicting life expectancy in people with recently diagnosed incurable cancer (Trajkovic-Vidakovic 2012). In addition, patients and their caregivers may be concerned about burdensome existential ruminations leading to psychological distress on both sides, with long-term risk of severe impairment in physical and psychological health among patients and caregivers, as well as declining resources of social support (Mehnert 2014; Singer 1999; Sklenarova 2015). Such developments within the family often promote conflict about responsibilities regarding decision making concerning therapeutic and everyday challenges. Economic consequences frequently comprise, for example, reduced family income or considerable out-of-pocket medical spending, leading to financial hardship for patients and their families (Elkin 2010; Zhang 2009). Owing to these strains, professional support gains extraordinary importance in alleviating physical discomfort and in contributing to improved quality of life among patients.

Description of the intervention

Palliative care is provided to reduce suffering and improve quality of life among patients and their caregivers. In recent years, the term 'early palliative care' was introduced to differentiate palliative care treatments applied early in the course of a life-threatening disease from palliative care delivered mainly with high symptom burden or in the terminal phase of illness, as was the established clinical practice. In cases of advanced cancer, early palliative care is provided alongside active disease treatment such as chemotherapy or radiotherapy.

A typical treatment protocol for investigators in early palliative care trials encompasses communication with the patient about illness and prognosis, symptom assessment and management, support for coping, and regular follow-ups. According to the latest consensus definition of palliative care, such treatment is called 'early' when it is administered within eight weeks of diagnosis of advanced cancer (Ferrell 2017). Other qualitatively identified elements include relationship and rapport building, development of coping skills, understanding of the illness, and discussion of available cancer treatments, including end-of-life planning (Yoong 2013). A prerequisite for palliative care in such an early situation is readiness of health care professionals to engage in coherent and empathetic communication with the patient (de Haes 2005; Dowsett 2000; Meyers 2003; Morrison 2004; Sinclair 2006). Early palliative care commonly is focussed on outlining realistic and attainable goals of treatment (van Mechelen 2013) and facilitating patient choices by providing adequate information and assessment of patient values and preferences with regard to advance care planning (Levy 2016). The inherent belief is that symptoms can be prevented or can be managed more easily when treated early, thereby improving the patient's quality of life. Most treatments involve education, evidence-based methods used for symptom control, and psychosocial support. In essence, early palliative care is based on a proactive attitude and usually is provided to patients without high symptom burden or unmet psychosocial needs.

Researchers have identified the following models of palliative care (Hui 2015a).

- *Solo practice model:* This model ascribes responsibility for cancer diagnosis and treatment as well as palliative care exclusively to the primary oncologist.
- *Co-ordinated care model:* As is often observed in common clinical practice, the primary oncologist in collaboration with the primary nursing team offers and co-ordinates supportive/palliative care. As part of this so-called congress model, primary providers refer patients to various specialists, who address domains of palliative care (other physicians, clinical nurse specialists, social workers, chaplains, psychotherapists, and clinical psychologists or psychiatrists).
- *Integrated care model:* In this model, oncologists routinely refer patients to specialist palliative care teams early in the disease trajectory, rather than excluding involvement of other specialists.

Regardless of the model selected, early palliative care can be delivered across a breadth of settings, including community centres, hospitals, and inpatient hospice units. Community hospice services may also support patients at an earlier stage of disease in the day care/outpatient setting.

Comparator arms in early palliative care trials generally consist of usual oncology care. This may include referral to or application of palliative measures at any time along the disease trajectory as initiated by an oncologist, patient, or family member. However, referral to or application of palliative measures are not usually offered actively to all patients.

How the intervention might work

With a focus on intensified doctor-patient communication, early palliative care may lead to higher levels of social support and may increase the likelihood of acceptance of the diagnosis and illness severity. These effects, along with the augmented satisfaction of the patient-physician relationship, may improve the patient's openness to symptom control and psychosocial interventions, thereby reducing distress. Reduced distress itself is associated with improved quality of life and is consistently associated with survival (Gotay 2008; Irwin 2013; Pinquart 2010). Furthermore, patients and family members undergoing early palliative care are better informed about treatment directives and end-of-life decisions, which promotes higher self-efficacy and a greater sense of control of decisions with respect to a person's individual values (McClain 2003). On the one hand, better symptom control and psychosocial function could promote better adherence with reasonable treatment plans. On the other hand, palliative care is linked to less aggressive cancer treatment, such as reduced use of questionable chemotherapy and less treatment time in intensive care units (Earle 2008). This tendency to de-escalate treatment intensity in final, irreversible health conditions, together with extension of outpatient and community palliative care services, is important for patients' well-being as well as to socioeconomics (Lowery 2013; Smith 2003).

Why it is important to do this review

Evidence for the effects of late palliative care is ambiguous because the time required to establish beneficial effects may be too short (El-Jawahri 2011; Gomes 2013; Higginson 2010; Zimmermann 2008). Palliative interventions applied early, around the time of diagnosis of incurable advanced cancer, may be more favourable for improving symptom and disease management (Levy 2016), leading some investigators to believe that a paradigm shift has occurred (e.g. Kamal 2016; Kelley 2010; Schenker 2015). To date, although several reviews on early palliative care interventions for patients with advanced cancer have been published (Bauman 2014; Davis 2015; El-Jawahri 2011; Gomes 2013; Greer 2013; Higginson 2010; Hui 2015b; Parikh 2013; Salins 2016; Smith 2012; Tassinari 2016; von Roenn 2011; Zambrano 2016; Zhi 2015; Zimmermann 2008), to our knowledge, no meta-analysis has been carried out. An overview of interventions applied within this framework has not been provided, and uncertainty remains about the general impact of such interventions on patient- and caregiver-related outcomes.

OBJECTIVES

To compare effects of early palliative care interventions versus treatment as usual/standard cancer care on health-related quality of life, depression, symptom intensity, and survival among adults with a diagnosis of advanced cancer.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and cluster-randomised controlled trials (cRCTs).

Types of participants

Patients were eligible if they had been given the diagnosis of a malignant tumour entity at an advanced stage (as assessed by the oncologist and based on disease stage and tumour type) and without curative treatment options (i.e. owing to metastatic disease or inoperability, or both). In accordance with information provided by the American Cancer Society (American Cancer Society 2013), we defined advanced cancers as "cancers that cannot be cured," and that, in the case of metastatic cancer, "have usually spread from where they started to other parts of the body." For all malignant entities, limited prognosis can be a common disease consequence and, therefore, constituted the main eligibility criterion for inclusion of participants in this review. Participant survival had to be estimated at two years or less. We did not include disabled long-term survivorship patients, although such patients may also be in need of early palliative care. Assessment of prognosis had to be based on disease stage as an objective clinical indicator, in conjunction with the clinician's estimation provided by the primary oncologist. We considered for inclusion only studies of adults, 18 years of age and older, and we excluded studies of adults given the diagnosis during childhood and of people already in the terminal phase of illness (predicted survival of less than three months with eligibility for hospice care) at study enrolment.

Types of interventions

As defined in a previous review (Zimmermann 2008), we included all types of professional palliative care services that provided or co-ordinated comprehensive care for patients at early advanced stages of cancer. Investigators had to state explicitly early palliative care intent, or this had to be reflected in the sample composition, that is, most participants had to be enrolled shortly after diagnosis of advanced disease. In addition, care had to be multi-dimensional (i.e. the intervention had to target at least the "physical" and "psychological" domains of quality of life). We excluded studies

evaluating the impact of only one domain of quality of care (e.g. medication for pain, psychological interventions for depression). We did not include stand-alone palliative therapies provided to modify the disease to prolong life (e.g. palliative chemotherapy) or relieve symptoms (e.g. palliative radiotherapy). We applied no restrictions on type of delivery (inpatient, outpatient) or place of consultation (clinic, patient's home). The active comparator was treatment as usual/standard cancer care (i.e. no systematic palliative treatment or delayed or late palliative care).

Types of outcome measures

We included two 'Summary of findings' tables as presented in the *PaPaS Author Guide* (AUREF 2012) and as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 4.6.6 (Higgins 2011a). The 'Summary of findings' table includes outcomes of quality of life, survival, depression, symptom intensity, and adverse events (see Summary of findings for the main comparison).

Primary outcomes

We included the following primary outcomes and corresponding measures.

- Health-related quality of life (e.g. measured by Functional Assessment of Cancer Therapy (FACT), City of Hope Quality of Life Questionnaire, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), McGill Quality of Life Questionnaire, 36-Item Short Form Health Survey (SF-36), or the Supportive Care Needs Survey (SCNS)).
- Survival.
- Depression (e.g. measured on Beck Depression Inventory (BDI), Hamilton Rating Scale for Depression (HAM-D), Hospital Anxiety and Depression Scale (HADS), Patient Health Questionnaire (PHQ-9), or Centre for Epidemiological Studies - Depression Scale (CES-D)).
- Symptom intensity (e.g. measured on Edmonton Symptom Assessment Scale (ESAS), or on Brief Pain Inventory (BPI)).

Outcomes had to be measured through self-report questionnaires, participant records or interviews that determined measures of adequate psychometric properties. Scales had to reflect continuous or time-to-event data for survival. The most relevant time points used to measure outcome were "medium term" (one to four months after initiation of early palliative care) for self-rated outcomes, and "long term" for survival.

Secondary outcomes

We assessed three categories of secondary outcomes.

- Caregiver burden as a caregiver-related outcome (e.g. measured on Caregiver Strain Index (CSI), Supportive Care Needs Survey for Partners & Caregivers (SCNS-P&C), BDI, HAM-D, PHQ-9, or CES-D).
- Healthcare utilisation (e.g. measured as length of hospital stay in days, number of outpatient attendances, direct or indirect medical resource use) as an economic outcome.
- Harms/adverse events (measured as the binary outcome "Any adverse event: yes/no").

During compilation of the review, we made the post-protocol decision to report results for outcomes that had not been prespecified in the protocol (namely, place of death, problems with medical interactions, satisfaction with care, and illness and understanding of prognosis). We did this so we could provide a more comprehensive overview of outcomes available for early palliative care.

Search methods for identification of studies

We prepared a highly sensitive literature search strategy by which to identify eligible studies. Joanne Abbott (JA), the Information Specialist for the Cochrane Pain, Palliative and Supportive Care Group, and Maria-Inti Metzendorf, of the Library of the Medical Faculty of Mannheim, Heidelberg University, supported drafting of search strategies. Two review authors (MWH and SE) documented the search process and the records, assessed potentially relevant studies, and made the final selection for inclusion and data extraction. We resolved disagreements by discussion and, in the case of eight studies, by consultation with an arbiter (MH).

Electronic searches

We searched the following electronic databases without language restrictions.

- CENTRAL (Cochrane Central Register of Controlled Trials) via the Cochrane Library (2016, Issue 9).
- MEDLINE (Medical Literature Analysis and Retrieval System Online) via OvidSP 1946 to 11 October 2016.
- Embase (Excerpta Medica dataBASE) via OvidSP 1974 to 11 October 2016.
- PsycINFO via OvidSP 1887 to 11 October 2016.
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO 1937 to 11 October 2016.
- OpenGrey (European Association for Grey Literature Exploitation - EAGLE) (www.opengrey.eu) via EXALEAD 1985 to 11 October 2016.

We performed free-text search of titles, abstracts, and keywords, as well as medical subject headings (MeSH), during searches. We ran the search from the earliest publication date possible in each database. We tailored searches to individual databases. Please see Appendix 1 for the full MEDLINE search strategy in OVID, and see Appendix 2, Appendix 3, Appendix 4, Appendix 5, and Appendix 6 for all other search strategies.

In addition, we searched citations of key review authors (Marie A Bakitas, Jennifer S Temel, Martin H N Tattersall, Camilla Zimmermann) via Web of Science and the "related article" feature of PubMed.

The Information Specialist for the Cochrane Pain, Palliative and Supportive Care Group conducted searches in CENTRAL, MEDLINE, Embase, and PsycINFO via the OvidSP interface, which was not available at Heidelberg University Hospital.

Searching other resources

Trial registers

We searched the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com/mrct), clinicalTrials.gov (www.clinicaltrials.gov), and the World Health Organization

(WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) on 11 October 2016, to identify additional completed or ongoing studies (search term: "palliative").

Reference lists

We checked the reference lists of 15 relevant reviews (Bauman 2014; Davis 2015; El-Jawahri 2011; Gomes 2013; Greer 2013; Higginson 2010; Hui 2015b; Parikh 2013; Salins 2016; Smith 2012; Tassinari 2016; von Roenn 2011; Zambrano 2016; Zhi 2015; Zimmermann 2008) and all potentially relevant records.

Correspondence

We contacted six authors of main studies and 21 investigators who were known to be carrying out research in this area for additional studies and to provide unpublished data.

Data collection and analysis

Selection of studies

During database searches, we downloaded all retrieved records, including abstracts, and compiled them by using the reference manager Endnote X6. We removed duplicate records electronically through Endnote X6 and manually after checking study authors, titles, and abstracts. As the next step, two review authors (MWH and SE) independently assessed search results and excluded records that obviously did not fulfil inclusion criteria. Raters linked together multiple reports of the same study. For remaining studies marked as potentially relevant by either review author, we obtained full-text documents and checked respective studies for eligibility. To ensure reproducibility of judgements regarding studies to be included, two unblinded raters (MWH and SE) again independently assessed full-text documents and agreed on which studies should be included in the review. To formally measure agreement between raters with regard to study inclusion, we calculated the simple kappa statistic to determine whether eligibility criteria should be reconsidered. When raters disagreed regarding study eligibility, we reached consensus or referred the question to an arbiter (MH). At this stage, we compiled a list of excluded records along with the primary reason for each exclusion (see Characteristics of excluded studies).

Data extraction and management

To extract data from each study, we set up and pilot-tested a data collection form and prepared coding instructions in accordance with the checklist proposed by Cochrane (Higgins 2011b, Table 7.3.a).

Two unblinded review authors (MWH, as topic area specialist, and SE, as methodologist) independently extracted data from published study reports and recorded them on a standard data collection form. We collected information on study design, setting, participants (including sample sizes), intervention details, outcomes (including time points), results, and missing data, as well as on risk of bias. We collated onto a single collection form data from multiple reports of the same study.

For meta-analysis of continuous outcome variables using standardised mean differences (SMDs), we extracted mean values and standard deviations of outcome measurements, as well as the number of participants included in each intervention group. For cluster-randomised trials, we applied the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011d). We registered effect estimates with confidence intervals and P values.

For time-to-death outcomes, we obtained estimates of log hazard ratios and their standard errors (Tierney 2007). Again, we resolved disagreements by discussion and, when necessary, by consultation with an arbiter (MH). For completion of study details and missing numerical results, we contacted study authors when necessary. One review author (SE) entered data suitable for pooling into Cochrane software Review Manager version 5.3 (RevMan 2014), and a second review author (MWH) verified entries. We report the characteristics of included studies in sufficient detail in the Characteristics of included studies table. We contacted study authors to request unpublished data for meta-analysis when required.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* and resolved disagreements by discussion (Higgins 2011c). When applying the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, we gave major priority to rating the certainty of evidence by assessing study outcomes with regard to risk of bias (Balshem 2011; Guyatt 2011a). We applied the Oxford Quality Score as the basis for eligibility (Jadad 1996), limiting inclusion to randomised controlled and cluster-randomised trials. Blinding of personnel was neither mandatory for inclusion nor necessary for risk of bias assessment because blinding usually is not feasible in palliative care studies (Piggott 2004); however, we assessed blinding of outcome assessment while assessing risk of bias (Movsisyan 2016a). Furthermore, high attrition rates did not automatically lead to exclusion, as these are to be expected in palliative care studies. Recruitment is a major challenge in the palliative care context, justifying more pragmatic methods such as cRCTs (median attrition rate at 40%, according to Zimmermann 2008). Rather, we regarded differences between intervention and control groups with reference to incomplete outcome data (Guyatt 2011a) as crucial criteria for ascribing risk of attrition bias. We decided to omit sample size as a criterion for risk of bias, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). Rather than assigning a priori judgement that small studies were at high risk of bias, we explored this assumption in our review by investigating small-study bias and by assessing sample size when grading the evidence for each outcome.

Furthermore, two unblinded independent review authors (MWH and SE) conducted a domain-based evaluation by completing a 'Risk of bias' assessment for each included study, using a data collection form that included seven specific domains: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. For cRCTs, we assessed risk of bias with regard to recruitment bias, baseline imbalance, loss of clusters, incorrect analysis, and comparability with individually randomised studies. We assessed the following for each study.

- Random sequence generation (checking for possible selection bias): We assessed the method used to generate the allocation

sequence as having low risk of bias (any truly random process, random number table, computer random number generator) or unclear risk of bias (method used to generate sequence not clearly stated). We used a non-random process to exclude studies that were at high risk of bias (odd or even date of birth; hospital or clinic record number).

- Allocation concealment (checking for possible selection bias): The method used to conceal allocation to interventions before assignment determines whether the intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed methods as having low risk of bias (telephone or central randomisation, consecutively numbered sealed opaque envelopes) or unclear risk of bias (method of allocation concealment not clearly stated). We excluded studies that did not conceal allocation and were therefore at high risk of bias (open list).
- Blinding of participants (checking for possible performance bias): We assessed the methods used to blind study participants from knowledge of which intervention a participant received. We assessed methods as having low risk of bias (study states that it was blinded and describes the method used to achieve blinding); unclear risk of bias (study states that it was blinded but does not provide an adequate description of how this was achieved). We considered studies in which participants were not blinded to have high risk of bias.
- Blinding of outcome assessment (checking for possible detection bias): We described all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. If applicable, we provided information related to whether the intended blinding was effective.
- Incomplete outcome data (checking for possible attrition bias): We assessed differences between intervention and control groups with reference to incomplete outcome data. Bias resulted only if the number lost was imbalanced between groups. However, large loss to follow-up in relation to the number of events always led to suspicion of a serious threat of bias (Guyatt 2011a).
- Selective outcome reporting (checking for possible reporting bias): We assessed outcomes reported and compared them with outcomes listed in initial study registrations or in published protocols. We suspected reporting bias if study reports failed to include results for prespecified key outcomes.
- Other bias: This included stopping early for benefit, use of non-validated outcome measures, carryover effects in cross-over studies, and recruitment bias in cRCTs.

Measures of treatment effect

To account for use of different scales across studies, we used SMDs as effect measures for continuous data for the primary outcomes health-related quality of life, depression, and symptom intensity. We analysed time-to-event data (survival duration) as death hazard ratio under the proportional hazards assumption that hazard ratio was constant across the follow-up period. With regards to secondary outcomes, we included results for caregiver burden as well as for healthcare and resource use as provided in the narrative review of a single study.

Unit of analysis issues

Unit of analysis issues may arise because in early palliative care studies, results may be presented for several periods of follow-up, and because in cRCTs, groups of participants instead of individual participants are randomised. We addressed the issue of several periods of follow-up by restricting measurement to a single point for each outcome, as described in Primary outcomes. For cRCTs, we adjusted sample sizes before calculating pooled effect estimates, if corresponding analyses did not properly account for the cluster design (e.g. by applying multi-level modelling, performing variance components analyses, or using generalized estimating equations) (Higgins 2011d). In cases of more than two parallel intervention arms, we planned to consider only two arms (preferably early palliative care arm vs standard care).

However, we did not find studies that included more than two arms.

Dealing with missing data

Whenever possible, we asked the original investigators to provide missing data. In palliative care settings, missing data may not be missing at random but may often indicate poor outcomes (i.e. death) (Hui 2013b; Hussain 2016). Thus, a simple replacement method did not seem adequate. We ultimately conducted available case analyses and included data only on cases for which results are known (Higgins 2011d).

Assessment of heterogeneity

We investigated variation in effects observed across studies by including a Chi^2 test within forest plots, with regards to the total number of identified studies. For further quantification of inconsistency across studies, we calculated the I^2 statistic, which directly reflects the percentage of variability in effect estimates that is due to heterogeneity rather than to chance (Deeks 2011). Higher percentages suggest greater observed heterogeneity. We expected heterogeneity due to different scales, patient populations, clinical settings, and types of interventions. As studies assessed the same outcomes but measured them in a variety of ways (e.g. different psychometric scales for health-related quality of life), we applied the SMD as the summary statistic in meta-analysis. For health-related quality of life, higher scores reflected benefit, but for depression and symptom intensity, higher scores indicated harm, and lower scores suggested benefit. To explore heterogeneity, we conducted a categorical subgroup analysis for 'models of early palliative care (solo practice, co-ordinated care, integrated care)'.

Assessment of reporting biases

We performed comprehensive database and manual searches, including searches of grey literature, to reduce the risk of reporting bias. As appropriate test power was not ensured owing to an insufficient number of included studies (< 10), we refrained from creating funnel plots and conducting Egger's test for funnel plot asymmetry (Egger 1997; Sterne 2011). In applying random-effects estimates of the intervention effect, we decided not to exclude small studies, as this might have led to an inappropriate reduction of studies in a field that is just emerging. We expect that in future updates of the review, when more studies on early palliative care have been published, we will be able to explore reporting biases by comparing fixed-effect and random-effects estimates or L'Abbé plots as a visual method of assessing differences in results of individual studies. Nevertheless, in case of small-study effects, we explored probable explanations, compared intervention effects, and cautiously considered sample size when grading and discussing the evidence for each outcome (Roberts 2015).

Data synthesis

To clarify the evidence for early palliative care interventions, we performed meta-analyses based on an inverse variance random-effects model with a sufficiently homogeneous group of studies, as planned (DerSimonian 1986). For quantitative synthesis, we combined study results on health-related quality of life, survival (unadjusted death hazard ratio), depression, and symptom intensity across studies using Review Manager 5.3 (RevMan 2014). Statistical analysis of study findings in meta-analyses included a combination of pair-wise comparisons regarding differences in anticipated continuous primary patient-related outcome data between early palliative care and the control condition. We expressed pooled effects as SMDs, or Hedges' adjusted *g*.

For cRCTs, we also conducted analysis at the level of the individual according to the generic inverse variance method. Provided that analysis in the primary study accounted for clustering of data (e.g. by multi-level modelling), we extracted direct estimates of the required effect measure. We controlled for unit of analysis error, which often leads to inadequate weighting of the cRCT in the meta-analysis due to overly precise confidence intervals. Therefore, we adjusted sample sizes to "effective sample sizes" for studies that did not properly account for the cluster design, as explicated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011d). To check for herd effects and contamination, we interpreted cRCT results in conjunction with effects identified by the individual RCTs included in the meta-analysis.

Certainty of the evidence

Two review authors (MWH, MH) independently rated certainty of evidence for the primary outcomes. We used the GRADE (Grades of Recommendation Assessment, Development and Evaluation) system to rank certainty of the evidence using GRADEprofiler Guideline Development Tool software (GRADEPro GDT 2015) and the guidelines provided in Chapter 12.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011). In determining the level of certainty regarding whether estimates of effects were correct, we first addressed risk of bias for individual studies. Individual studies achieved low risk of bias when most or all criteria attained a low level of risk and any violations were not crucial. Studies that exhibited one violation of crucial importance (i.e. high risk of bias) with regard to a point estimate provided evidence of limited certainty and therefore were downgraded in the next step (Guyatt 2011a). Second, we applied the GRADE system of rating the certainty of evidence for each outcome across studies (Balshem 2011).

The GRADE approach applies five considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess certainty of the body of evidence for each outcome. The GRADE system uses the following criteria for grade of evidence assignment.

- **High certainty**: we are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate certainty**: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;
- **Low certainty**: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;
- **Very low certainty**: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We decreased grade if we noted:

- serious (-1) or very serious (-2) limitations in study quality;
- important inconsistency (-1);
- some (-1) or major (-2) uncertainty about directness;
- imprecise or sparse data (-1); or
- high probability of reporting bias (-1).

As suggested by the GRADE Working Group (Guyatt 2011a), we were generally conservative in downgrading and considered risk of bias in the context of other limitations. We made close-call situations explicit. For transparency, we explained in footnotes in the 'Summary of findings' table (Summary of findings for the main comparison) rationales for downgrading according to the GRADE system.

'Summary of findings' table

We included a 'Summary of findings' table to present the main findings in a transparent and simple tabular format. In particular, we included key information regarding certainty of the evidence, magnitude of effect of interventions examined, and the sum of available data on key outcomes.

Subgroup analysis and investigation of heterogeneity

For prespecified explanatory variable 'models of early palliative care (solo practice, co-ordinated care, integrated care)', we conducted a categorical subgroup analysis to identify organisation as a potential effect modifier on the basis of seven included studies. Because we included an insufficient number of studies (n = 2; Maltoni 2016; Temel 2010), which drew on a population with a homogeneous malignancy, we decided that we would not conduct a similar analysis for the second hypothesised explanatory variable 'samples with a single type of tumour versus samples with various tumour types'. Owing to an insufficient number of included studies (n < 10), we did not perform a meta-regression to explore a dose effect of the intervention on outcome variables. This decision reflects accordance with current interpretations of guidelines for systematic reviews and meta-analyses, "discouraging statistical investigations such as subgroup analyses and meta-regression, rather than simply adopting a cautious approach to their interpretation, unless a large number of studies is available" (Thompson 2002). Nevertheless, we evaluated heterogeneity by computing the I^2 statistic as described above and interpreted results with regard to the direction of effect across studies. We regarded an I^2 statistic exceeding 75% as considerable (Higgins 2003). Eventually, in the discussion, we extensively commented on risk of bias findings and degree of heterogeneity within each outcome comparison.

Sensitivity analysis

Owing to an insufficient number of included studies (n < 10), we did not perform sensitivity analysis by re-running the meta-analysis while excluding one study at a time to identify outlying studies. Consequently, we did also not incorporate results of the risk of bias assessment in sensitivity analyses limited to high-quality studies. However, we conducted a sensitivity analysis on study design as

a covariate (RCT vs cRCT) to investigate the robustness of the pooled effect estimate. We highlight the observational character of results of this sensitivity analysis and avoided presenting definitive conclusions for early palliative care, as it represents a still emerging interventional approach with few studies published to date.

RESULTS

Description of studies

See also the Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; and Characteristics of ongoing studies tables.

Results of the search

Searches of six databases (see Electronic searches) yielded 21,475 records. Searches of other resources (trial registers, systematic reviews, conference proceedings, journal eTOC alerts, contact with content experts) revealed 1719 additional records that appeared to meet the inclusion criteria. We therefore obtained a total of 23,190 records.

Once we had removed duplicates, we had a total of 16,999 records. We excluded 16,886 records on the basis of reviews of reviews of titles and abstracts. We obtained the full text for the remaining 113 records. We excluded 21 studies (29 records) (see Characteristics of excluded studies) and added 10 studies (20 records) to Characteristics of studies awaiting classification. We identified 20 ongoing studies (26 records) (see Characteristics of ongoing studies).

Use of a simple kappa statistic for interrater variation with regard to study inclusion amounted to κ = 0.60, which indicated good agreement (Higgins 2011b). In summary, we included seven studies reported in 38 references (31 full papers and seven trial registry entries, one per study), ranging from one to 11 full papers per study (Bakitas 2009, six full papers; Bakitas 2015, five full papers; Maltoni 2016, two full papers; McCorkle 2015, one full paper; Tattersall 2014, one full paper; Temel 2010, 12 full papers; Zimmermann 2014, four full papers). For a further description of our screening process, see the study flow PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram (Liberati 2009), depicted in Figure 1.

Figure 1. Screening process diagram (as recommended by the PRISMA statement).

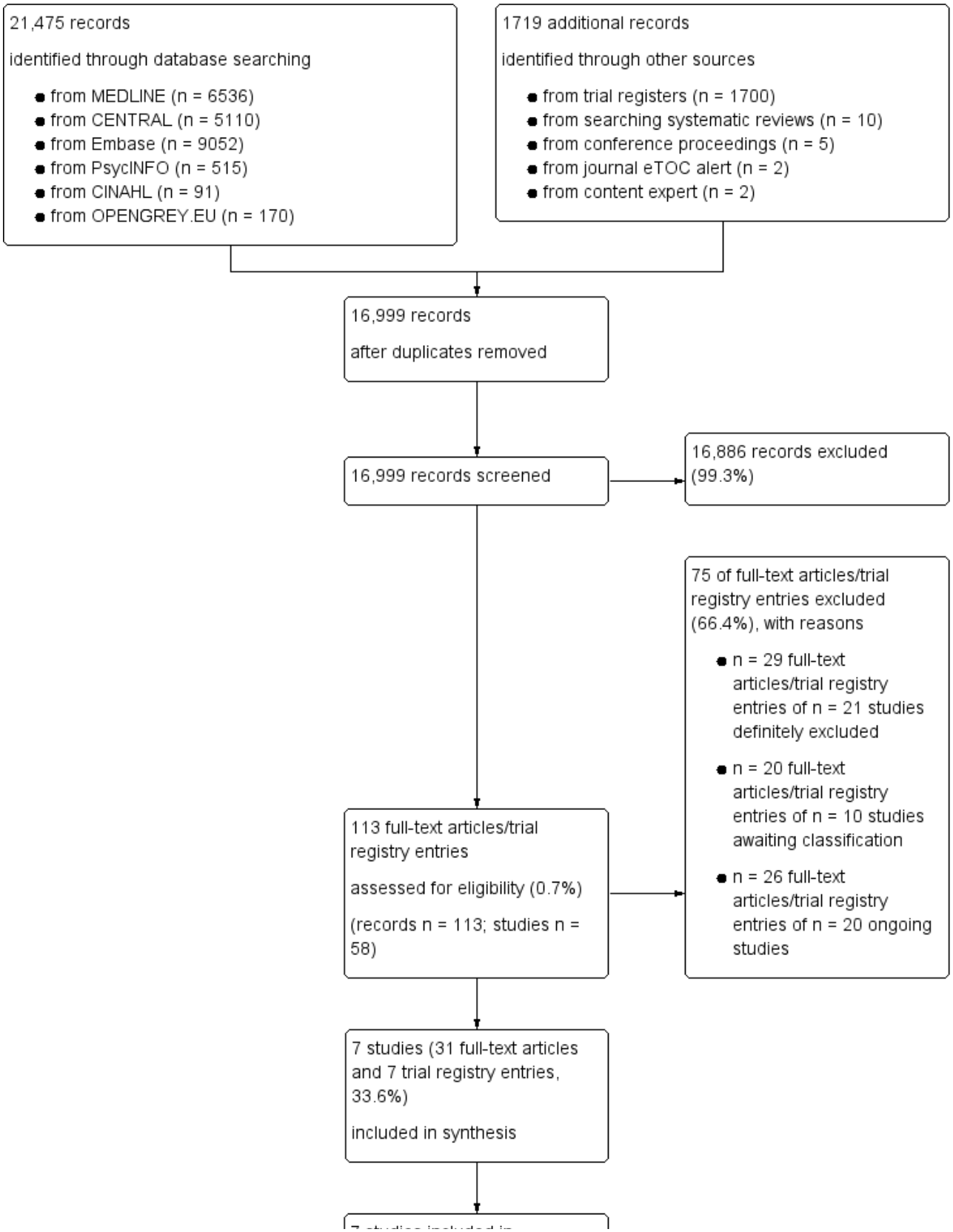
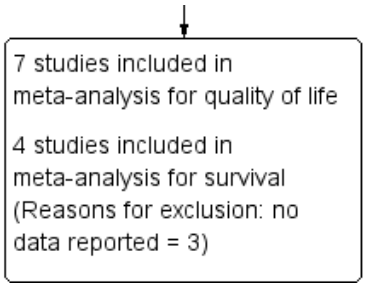


Figure 1. (Continued)



Included studies

Designs

Five of the seven studies were prospective RCTs with participants as units of randomisation and a single intervention and a single comparator arm (Bakitas 2009; Bakitas 2015; Maltoni 2016; Tattersall 2014; Temel 2010). Bakitas 2015 applied a so-called fast-track RCT design, randomising participants to receive concurrent palliative care with standard oncology care shortly after diagnosis of advanced or progressive disease (early group), or three months later (delayed group). Two studies were cluster-randomised trials treating oncology clinics as units of randomisation and participants as units of inference (McCorkle 2015; Zimmermann 2014).

Sample sizes

Unadjusted sample sizes varied between 120 and 461 participants. Recruitment length ranged from 22 to 51 months. In total, we analysed data from studies involving 1614 participants. Bakitas 2009 and Bakitas 2015 provided data for 320 caregivers in total. Maltoni 2016 measured family satisfaction with end-of-life care but has not yet published caregiver results. Zimmermann 2014 provided data for 151 caregivers in total (McDonald 2016). Six of the seven studies were guided by power calculations (details in Characteristics of included studies): Bakitas 2009 powered on quality of life, symptom intensity, and depression, and Maltoni 2016 and Temel 2010 on the Trial Outcome Index (TOI), that is, pancreatic/lung cancer-specific symptom intensity and physical and functional well-being. Bakitas 2015 powered on quality of life and depression, whereas Zimmermann 2014 powered on quality of life only. Tattersall 2014 powered on a 0.5 standard deviation (SD) but did not indicate a primary outcome. McCorkle 2015 did not provide a power calculation. Four of the six studies drawing on power calculations were underpowered at recruitment stage, most commonly owing to slower enrolment than was projected. Two studies (Temel 2010; Zimmermann 2014) reached adequate power by amending the protocol.

Study populations

Five of the seven studies investigated populations with heterogeneous tumour entities (Bakitas 2009; Bakitas 2015; McCorkle 2015; Tattersall 2014; Zimmermann 2014). In contrast, Temel 2010 focussed on exclusive enrolment of participants with metastatic non-small cell lung cancer, whereas Maltoni 2016 focussed on exclusive enrolment of participants with metastatic pancreatic cancer. Four studies investigated caregivers along with participants (Bakitas 2009; Bakitas 2015; Maltoni 2016; Zimmermann 2014). Mean age ranged from 60 to 67 years. Across all studies, investigators included slightly higher numbers of male compared with female participants, except in two studies, in which women constituted the majority of participants (McCorkle 2015, Zimmermann 2014). In five studies, approximately two-thirds of all participants were married or were living with a partner. This proportion was slightly lower in two studies (McCorkle 2015; Temel 2010). In three studies, the vast majority of participants (> 85%) stated that they had received nine or more years of education. A similar proportion (> 75%) was unemployed. Three studies did not provide data on education levels of nine years or below nor on employment status (Maltoni 2016; Tattersall 2014; Temel 2010).

Setting

Five studies took place in the United States (US) (three in predominantly rural areas in New Hampshire, Connecticut, and Vermont; one in the metropolitan area of Boston; one at Yale-New Haven). One study was conducted in Toronto, Canada (metropolitan area); one in Italy (multiple sites); and one in Sydney, Australia (metropolitan area) (see Characteristics of included studies table for details). Although two US studies recruited from National Cancer Institute-designated (comprehensive) cancer centres solely, and one recruited from a tertiary referral hospital, the remaining two US studies additionally recruited from a Veterans Affairs Medical Center. Both the Canadian study and the Australian study recruited from tertiary referral hospitals. For the Maltoni 2016 trial, investigators recruited most participants from palliative clinics of tertiary centres, and a minority were enrolled in smaller community cancer centres (unpublished data received upon study author request).

Early palliative care interventions

Solo practice model

We did not identify any studies providing early palliative care based on a solo practice model.

Co-ordinated care model

Three studies followed the co-ordinated care model in establishing an advanced practice nurse as a co-ordinator and in linking care from different specialist disciplines (Bakitas 2009; Bakitas 2015; McCorkle 2015). In the ENABLE II study, Bakitas 2009 provided outpatient palliative care. Specifically, two advanced practice nurses with palliative care specialty training provided case management and education via a manualised, telephone-based approach for participants in the intervention group. The intervention comprised four initial structured educational and problem-solving telephone sessions provided on a weekly basis (education manual: *Charting your Course: An Intervention for People and Families Living With Cancer*) and at least monthly telephone follow-up sessions thereafter until the participant died or the

study ended. Investigators applied problem-solving management on the basis of systematic distress assessment using the Distress Thermometer and a cut-off > 3. When concerns were identified, participants were encouraged to contact oncology or palliative care clinical teams.

In the ENABLE III study (Bakitas 2015) for outpatient palliative care, all participants received usual oncology care directed by a medical oncologist. The intervention comprised anticancer and symptom control treatments and consultation with oncology and supportive care specialists, including a clinical palliative care team, which was provided whenever requested, regardless of group assignment. The intervention followed a telehealth concurrent palliative care model, commencing within 30 to 60 days of an advanced cancer diagnosis, cancer recurrence, or progression. The model was based on an initial in-person, standardised outpatient palliative care consultation with a board-certified palliative care clinician and six structured weekly telephone coaching sessions provided by an advanced practice nurse, again using a manualised curriculum *Charting Your Course: An Intervention for Patients With Advanced Cancer*. Sessions one to three focussed on problem solving, symptom management, self-care, identification and co-ordination of local resources, communication, decision making, and advance care planning. Sessions four to six comprised Outlook, a life-review approach that encourages participants to frame advanced illness challenges as personal growth opportunities; after completion of the six *Charting Your Course* sessions, monthly follow-up calls reinforced prior content and identified new challenges or care co-ordination issues.

In the McCorkle 2015 study for outpatient palliative care, all participants received usual oncology care directed by a medical oncologist. This study was based on a 10-week standardised intervention for the experimental group delivered by different members of each team, which included monitoring participants' status, providing symptom management, executing complex care procedures, teaching participants and family caregivers, clarifying the illness experience, co-ordinating care, responding to the family, enhancing quality of life, and collaborating with other providers. Advanced practice nurses at the clinics initially contacted participants within 24 hours and maintained weekly phone and scheduled in-person contacts (five clinic visits and five telephone calls). Members of each disease-specific multi-disciplinary team worked together as a palliative care unit, with each member taking on different functions to ensure that all components of the intervention were addressed. Furthermore, the clinic advanced practice nurse oversaw co-ordination and implementation.

Integrated care model

Four studies followed the integrated care model. In the Maltoni 2016 study, participants assigned to the interventional arm underwent systematic symptom assessment during an appointment scheduled with a palliative care specialist, who applied a predefined checklist during the consultation. Topics on the checklist were adapted from the Temel 2010 trial. Participants met with a member of the palliative care team within two weeks of enrolment and were seen thereafter every two to four weeks until death. Appointments and interventions were oriented by general palliative care guidelines introduced by the US National Consensus Project. The palliative care specialist who regularly saw interventional arm participants prescribed drugs and requested other interventions tailored to participants' physical, psychological, and spiritual needs. However, recommendations made by the palliative care expert on decision-making processes had to be shared with the attending oncologist.

The study by Tattersall 2014 provided outpatient palliative care via meetings between the participant and a palliative care nurse consultant member of the hospital palliative care team. The nurse outlined available palliative care services, including advice about symptom control, and offered to arrange review by a palliative care physician. Contact details for the palliative care service were provided. The palliative care nurse offered to telephone the participant monthly to check on that individual's well-being; if the participant preferred, the nurse provided contact details for the participant's use. Standard oncological care was given according to the oncologist's recommendations.

In the Temel 2010 study, participants in the intervention group met with a member of the palliative care team, which consisted of board-certified palliative care physicians and advanced practice nurses, within three weeks after enrolment and at least monthly thereafter in the outpatient setting until death. Additional visits with the palliative care service were scheduled at the discretion of participant, oncologist, or palliative care provider. General guidelines for palliative care visits in the ambulatory setting were adapted from the National Consensus Project for Quality Palliative Care and were included in the study protocol. Investigators paid specific attention to assessing physical and psychosocial symptoms, establishing goals of care, assisting with decision making regarding treatment, and co-ordinating care on the basis of individual needs of the participant. All participants continued to receive routine oncological care throughout the study period.

In a cRCT that examined care provided in outpatient clinics, as well as inpatient and home care, Zimmermann 2014 followed a multi-disciplinary approach to address physical, psychological, social, and spiritual needs. At outpatient clinics, participants consulted with palliative care physicians and nurses during routine visits once monthly and more often if necessary. Routine structured symptom assessment conducted during every visit was combined with routine psychosocial assessment and discussion of goals of care, of participant and family support needs, and of participant and family coping and psychological distress. Advance care planning was discussed according to participant and family readiness. Palliative care nurses provided routine telephone follow-up after each visit. A 24-hour on-call service was explained during the first visit and was provided throughout the study. The hospital service included direct access to the palliative care unit for symptom management and follow-up by the palliative care team when the participant was admitted to non-palliative care unit services. Within home care, community care access centre services were explained and offered during the first visit, and need was reassessed at each visit. The availability of a home palliative care physician was explained during the first visit, and this service was offered when Eastern Cooperative Oncology Group (ECOG) performance status exceeded a score of 3, or when the participant requested the service.

Comparators

Active comparators in the included studies constituted free access to all oncology and supportive services, including referral to other palliative care services (Bakitas 2009), and usual oncology care directed by a medical oncologist. This consisted of anticancer and

symptom control treatments and consultation with oncology and supportive care specialists, including a clinical palliative care team (Bakitas 2015). In the Maltoni 2016 study, participants assigned to the standard arm were scheduled to meet with the palliative care team only when participants themselves, their families, or the attending oncologist requested an appointment.

In the Australian study and in one US study, control participants were referred to the palliative care service when recommended by the oncologist (McCorkle 2015; Tattersall 2014). Similarly, in the study by Temel 2010, participants in the control condition met with the palliative care service only on their own, their family's, or the oncologist's request. In the fifth study, the control group followed an approach that mainly addressed physical symptoms and was provided in outpatient clinics, as hospital service, or as in-home care (Zimmermann 2014).

Outcomes

Six of the seven studies listed quality of life as a primary outcome, although Bakitas 2015 did not differentiate between primary and secondary outcomes and also targeted quality of life as a study outcome. Only Temel 2010 and Zimmermann 2014 named quality of life as single primary outcome. The remaining four studies listed more than one primary outcome, including symptom intensity, resource use, depression, unmet needs, emotional distress, health distress, self-rated health, functional status, and/or survival (Bakitas 2009; Maltoni 2016; McCorkle 2015; Tattersall 2014). Investigators included the following as secondary outcomes: depression, anxiety, self-efficacy, uncertainty, survival, participant interaction with nurses and doctors, quality of care, family satisfaction with (end-of-life) care, caregiver burden, aggressiveness of (end-of-life) care/number of lines of chemotherapy, experience of end-of-life care, use of healthcare resources, and place of death.

Funding sources

The US studies (Bakitas 2009; Bakitas 2015; Temel 2010) were funded by the National Cancer Institute (NCI), the American Society of Clinical Oncology (ASCO), philanthropic gifts, and the National Institute for Nursing Research (NINR). The Australian study (Tattersall 2014) was funded by the National Health and Medical Research Council (NHMRC). The US cRCT (McCorkle 2015) was funded by the NINR, and the Canadian cRCT (Zimmermann 2014) by the Canadian Cancer Society and the Ontario Ministry of Health and Long Term Care. The Italian study Maltoni 2016 was funded by the Italian Ministry of Health.

Excluded studies

We excluded from the review 21 studies that we had initially rated as potentially relevant. We excluded most of these studies because interventions did not demonstrate genuine early palliative care intent (n = 10). We excluded other studies owing to the absence of a multi-dimensional approach (n = 7), other than predefined primary outcomes (n = 1), quasi-experimental design (n = 1), withdrawal from the study (n = 1), and implementation instead of clinical study design (n = 1). For an overview of excluded studies, please refer to the Characteristics of excluded studies table.

Studies awaiting classification

We identified 10 studies that had been completed at the time of the search. However, these studies are awaiting classification, as they have not yet been published. For an overview of studies awaiting classification, please refer to the Characteristics of studies awaiting classification table.

Ongoing studies

We identified 20 ongoing studies. For an overview of these studies, please refer to the Characteristics of ongoing studies table.

Risk of bias in included studies

We assessed risk of bias using the Cochrane 'Risk of bias' tool (see Figure 2 and Figure 3) (Higgins 2011c). In formulating summary assessments of risk of bias for each important outcome (across domains) within and across trials, we applied the approach introduced by Higgins 2011e (Figure 2; Figure 3). Across trials, we identified high risk of bias for all outcomes (for health-related quality of life and symptom intensity due to selection (insufficient allocation concealment), performance, detection, attrition, and reporting biases; for survival due to selection (insufficient allocation concealment), performance, and attrition biases; and for depression due to selection (insufficient allocation concealment), performance, detection, and reporting biases).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

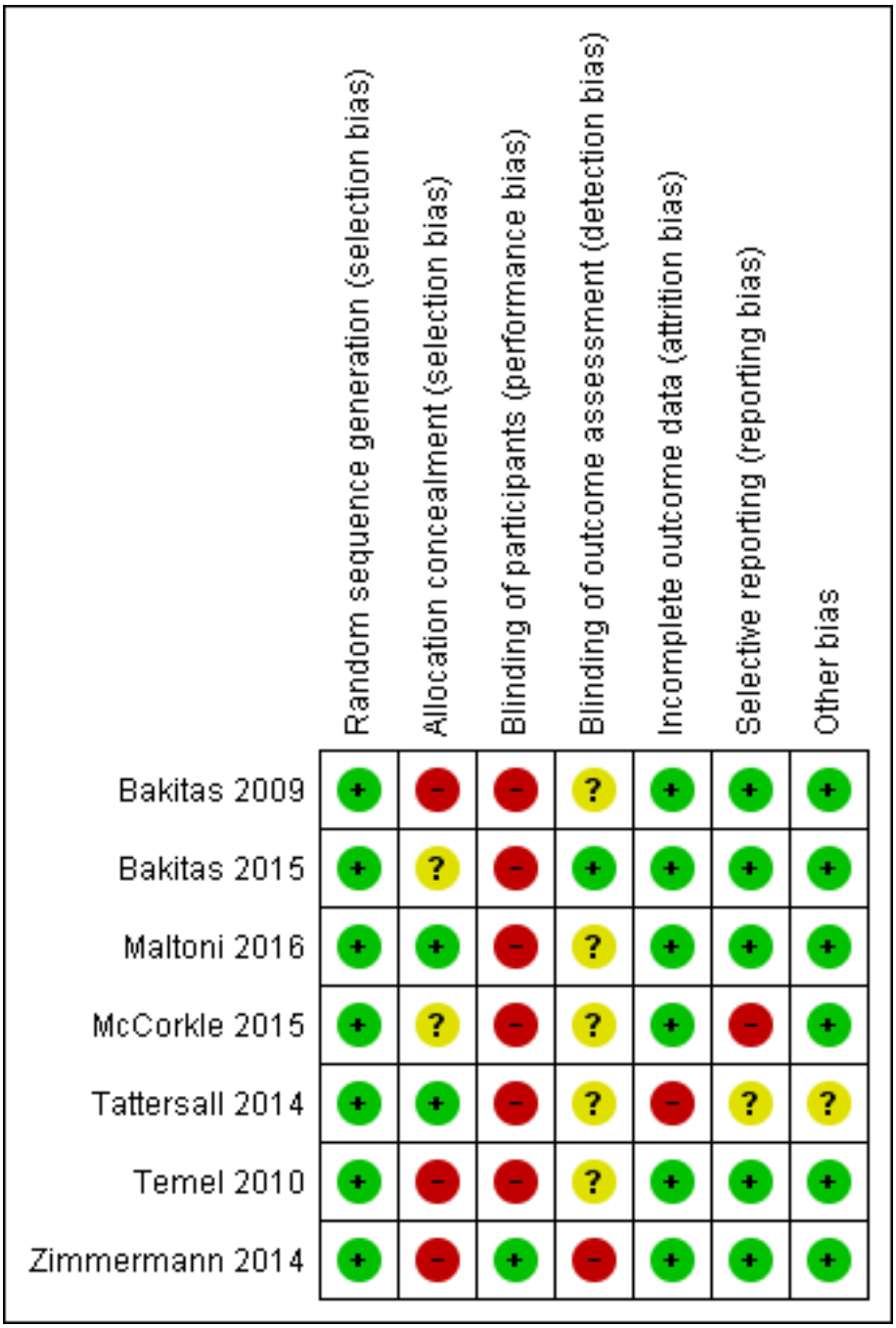
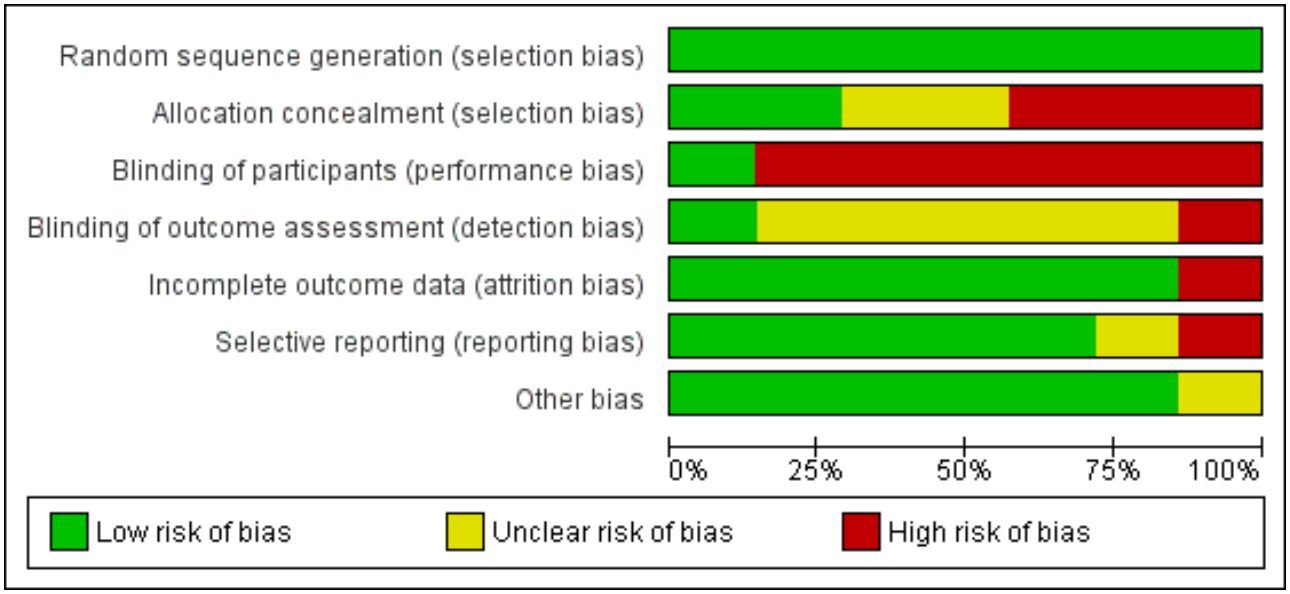


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation

All seven studies were randomised and adequately described the method used to generate the random sequence; therefore, we judged these studies to be at low risk of bias for this domain. Most studies applied computer-generated random numbers. We did not identify any studies at high or unclear risk of bias for this domain.

Allocation concealment

Authors of four studies adequately described allocation concealment of the sequence in the main publication (Bakitas 2009; Maltoni 2016; Tattersall 2014; Zimmermann 2014). For the Temel 2010 study, we received information from the principal investigator upon request. For Bakitas 2015 and McCorkle 2015, risk of bias remained unclear owing to insufficient information. We considered two studies to be at low risk of bias for this domain (Maltoni 2016; Tattersall 2014), although we noted high risk of bias for the three remaining studies: Bakitas 2009 and Temel 2010 did not conduct allocation concealment. As investigators randomised clusters before obtaining consent of individuals, we classified the Zimmermann 2014 study to be at high risk for this domain. Of note, study authors discussed this limitation in the main publication of the study.

Blinding

As explicated in the Methods, we did not include blinding of personnel in our risk of bias assessment owing to infeasibility and inappropriateness in the context of palliative care. We considered this infeasibility of personnel blinding to be a methodological factor that applied similarly to all included studies. However, we included blinding of participants and blinding of outcome assessment.

Blinding of participants

In terms of blinding of participants, we judged six studies (Bakitas 2009; Bakitas 2015; Maltoni 2016; McCorkle 2015; Tattersall 2014; Temel 2010) to be at high risk of bias for this domain. In the Zimmermann 2014 trial, investigators ensured blinding of participants within the framework of a cluster-randomised trial, so we judged this trial be at low risk of bias.

Blinding of outcome assessment

With respect to blinding of outcome assessment, five of the seven primary reports on included studies provided no details of this. Thus, we judged these studies (Bakitas 2009; Maltoni 2016; McCorkle 2015; Tattersall 2014; Temel 2010) to be at unclear risk of bias for this domain. Zimmermann 2014 did not blind investigators. We considered this study to be at high risk of detection bias. Bakitas 2015 explicitly mentioned that outcome assessors were blinded. We considered this study to be at low risk of detection bias.

Incomplete outcome data

Six of the seven included studies reported attrition rates in intervention and control groups that were approximately identical. As a characteristic of patient populations with advanced cancer, these rates were rather high. The most important reasons given across studies were decline in performance status, death, exhaustion, or cognitive impairment. We judged these six studies to be at low risk of bias for this domain. We had difficulty rating risk of attrition bias for the Zimmermann 2014 study, in which higher attrition in the intervention group reached borderline significance over the control group. Thus, in a close-call situation, we decided to assume that risk for attrition bias was low. One study (Tattersall 2014) reported seriously high attrition across intervention and control groups, indicating high risk of attrition bias.

Selective reporting

We observed few inconsistencies between outcomes listed in study registrations and those reported in publications for three studies. However, all key outcomes were reported and some included studies were published only recently, so we judged these three to be at low risk of bias for this domain. Bakitas 2009, Maltoni 2016,

and Temel 2010 reported outcomes in accordance with the a priori study registration. Zimmermann 2014 did not provide information on results for registered secondary outcomes of Caregiver Quality of Life Index-Cancer (CQOL-C) and the Short Form (SF)-36 Survey. However, researchers reported all key outcomes, and we favoured low risk of bias.

The Bakitas 2015 publication did not differentiate between primary and secondary outcomes. However, investigators reported all key outcomes. We made a close-call decision favouring low risk of bias. Tattersall 2014 was not registered until after recruitment had been opened, and so we judged this study to be at unclear risk of bias for this domain.

For McCorkle 2015, we detected high risk of reporting bias: Uncertainty (MUIS-C) described as a single primary outcome in clinicaltrials.gov registration was reported by study authors as a secondary outcome. Published results of this study included additional secondary outcomes that had not been preregistered.

Other potential sources of bias

Overall, we judged six studies to be at low risk of other bias, and one study to be at unclear risk for this domain.

In sum, we did not identify other potential sources of major bias in five studies, and so we judged them to be at low risk of bias for this domain. All five studies measured participant characteristics and outcomes at baseline, and four studies found no substantial differences between intervention and control groups.

For McCorkle 2015, results showed statistically significant differences between arms at baseline with respect to age, gender, and comorbidity. Given this baseline imbalance, recruitment bias may be present. We made a close-call decision favouring low risk of other bias, as high risk of selection bias was already detected.

In Zimmermann 2014, results revealed imbalance between intervention and control groups at baseline, exhibiting a tendency for higher outcome measure scores (for FACIT-Sp at $P = 0.03$; for ESAS at $P < 0.001$; for FAMCARE-P16 at $P < 0.001$) in the intervention group. For quality of life and family satisfaction with care, this implied that improvements were more difficult to attain for the intervention group and therefore negatively biased effect size. For symptom intensity, worsening might have been more likely for the control group, entailing a positively biased effect size. Also a larger number of participants with genitourinary cancers were included in the control group at baseline. However, we judged this study to be at low risk of bias.

Tattersall 2014 found baseline differences between groups in time since initial cancer diagnosis (shorter time for intervention group) and in oncologists' estimate of likely survival (better prognosis for intervention group). However, researchers controlled for these variables in their analyses, and in the light of a close-call situation, we decided not to rate down for imbalance bias but stated unclear risk of bias.

For Bakitas 2009, Bakitas 2015, Maltoni 2016, and Temel 2010, we found no evidence indicating other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Early palliative care for adults with advanced cancer

We report here synthesis results for the following prespecified primary outcomes: health-related quality of life, survival, depression, and symptom intensity. For all outcomes across all seven included studies, data could be incorporated into syntheses as long as the given study measured the outcome. Apart from pooled effect estimates, we also report results for individual studies. At this point, we underline that we have to interpret pooled effect estimates with caution owing to low certainty of the current evidence.

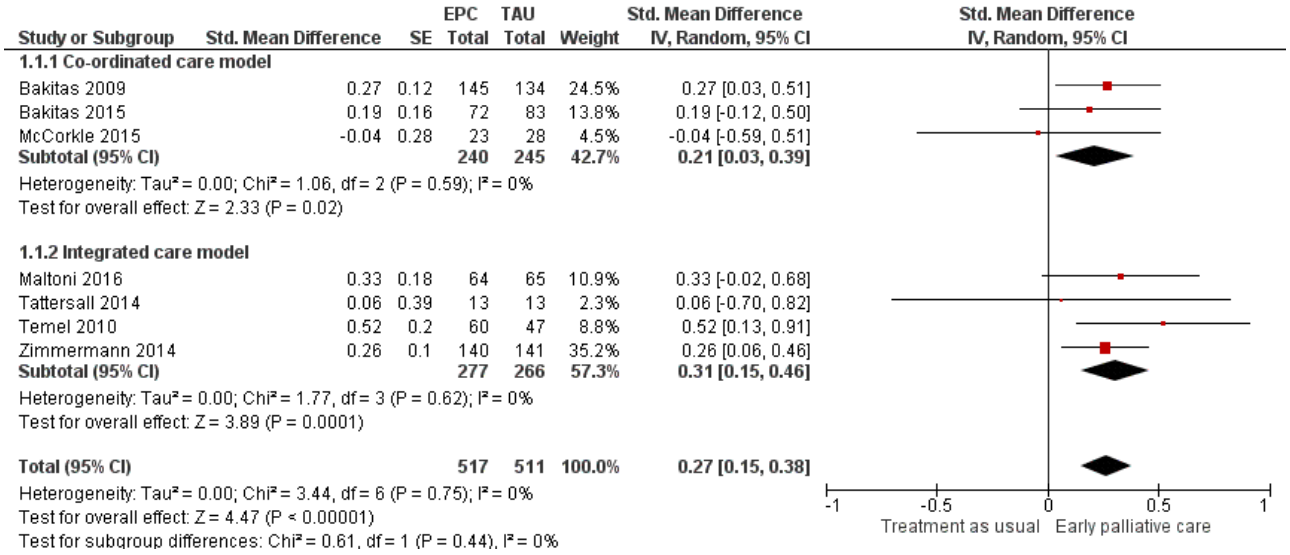
For prespecified secondary outcomes (caregiver burden, healthcare utilisation, and harms/adverse events), we could not find a sufficient number of studies, warranting synthesis in meta-analysis. Instead, we report data in a narrative format. We found data on all prespecified outcomes of interest, although pooling of effects was possible only for primary outcomes. For an overview of results, please see Summary of findings for the main comparison, as well as the risk of bias assessment presented in Figure 2.

Concerning time points, we identified five RCTs as relying on predefined time points for the outcomes of health-related quality of life, depression, and symptom intensity at 12 weeks (Bakitas 2015; Maltoni 2016; McCorkle 2015; Temel 2010; Zimmermann 2014). Therefore, we calculated SMDs for these studies on the mean difference at 12 weeks. Two studies applied mixed-effects models for repeated measures on longitudinal data (Bakitas 2009; Tattersall 2014). For these studies, we used resulting mean differences over time in calculating SMDs.

Primary outcome: health-related quality of life

Pooled data from seven studies (five RCTs, two cRCTs), with 1028 analysed participants (sample size for available case analysis at T1) available for the relevant comparison, showed that those receiving early palliative care had significantly higher quality of life than those receiving usual care (SMD 0.27, 95% CI 0.15 to 0.38) (Analysis 1.1; Figure 4). The effect size is small by conventional criteria. We combined different scales measuring this outcome of interest across studies by applying SMDs. Positive SMDs reflect benefit (better quality of life); negative SMDs indicate harm (lower quality of life). We found that researchers used seven different scales for measuring health-related quality of life as an outcome in the included studies (Functional Assessment of Chronic Illness Therapy for Palliative Care, FACIT-Pal, in Bakitas 2009 and Bakitas 2015; Trial Outcome Index, TOI, of the Functional Assessment of Cancer Therapy-Hepatobiliary, FACT-Hep, in Maltoni 2016; Functional Assessment of Cancer Therapy-General, FACT-G, in McCorkle 2015; McGill Quality of Life, McGill QOL, in Tattersall 2014; TOI of the Functional Assessment of Cancer Therapy-Lung, FACT-L, in Temel 2010; and Functional Assessment of Chronic Illness Therapy for Spiritual Well-Being, FACIT-Sp, in Zimmermann 2014). Zimmermann 2014 additionally used the Quality of Life at the End of Life, QUAL-E, on which, in contrast to findings for the FACIT-Sp, the difference between groups in change scores at 12 weeks was borderline significant ($P = 0.05$).

Figure 4. Forest plot of comparison: 1 Health-related quality of life, outcome: 1.1 Health-related quality of life.



Within the GRADE approach, we downgraded the certainty of evidence for health-related quality of life to low owing to high risk of bias at study level across studies (-2 points due to very serious limitations in study quality: high risk of bias for selection (insufficient allocation concealment), performance, detection, attrition, and reporting biases) (Summary of findings for the main comparison).

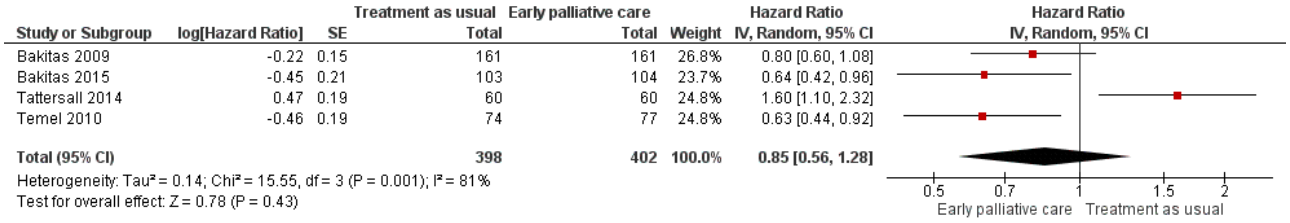
Results of individual studies

Bakitas 2009 found higher quality of life as measured with FACIT-Pal for the nurse-led early palliative care group compared with the control group (mean overall treatment difference of 4.6 with a standard error (SE) of 2), which translates into an SMD or small effect size of g = 0.27 with an SE of 0.12. At three months, Bakitas 2015 reported no significant differences between groups that responded to the FACIT-Pal (estimated mean 129.9 with 95% CI 126.6 to 133.3 for the early palliative group vs 127.2 with 95% CI 124.1 to 130.3 for the delayed group), which translates into an SMD or non-significant effect size of g = 0.19 with an SE of 0.16. Maltoni 2016, when applying the TOI of the FACT-Hep, detected higher quality of life for the early palliative care group than for the control group at three months (estimated mean 84.4 with a standard deviation (SD) of 16.3 for early palliative care vs 78.1 with an SD of 21.3 for control), which translates into an SMD or effect size of g = 0.33 with an SE of 0.18. At three months, McCorkle 2015 found no significant differences between groups that responded to the FACT-G (estimated mean 82.1 with an SD of 18.1 for the early palliative group vs 82.7 with an SD of 14.5 for the control group), which translates into an SMD or non-significant effect size of g = -0.04 with an SE of 0.28. Tattersall 2014, using the McGill QOL total score, identified no significant differences between groups at three months (estimated mean 5.2 with an SD of 0.8 for the early palliative group vs 5.2 with an SD of 0.7 for the control group), which translates into an SMD or non-significant effect size of g = 0.06 with an SE of 0.39. Temel 2010 reported that participants assigned to early palliative care achieved significantly better quality of life on the TOI of the FACT-L at three months (estimated mean 59.0 with an SD of 11.6 for the early palliative group vs 53.0 with an SD of 11.5 for the standard care group), which translates into an SMD or effect size of g = 0.52 with an SE of 0.2. Zimmermann 2014 found no significant differences between groups that responded to the FACIT-Sp (mean difference of 1.6 with an SD of 14.5 for the early palliative group vs -2.00 with an SD of 13.6 for the control group), which translates into an SMD or non-significant small effect size of g = 0.26 with an SE of 0.1.

Primary outcome: survival (death hazard ratio)

Pooled data from four studies (four RCTs), with 800 analysed participants available for the relevant comparison, showed that the death hazard ratio for those receiving early palliative care did not differ significantly from that for participants receiving usual care (hazard ratio (HR) 0.85, 95% CI 0.56 to 1.28) (Analysis 1.3; Figure 5). Death HRs below 1.0 reflect longer survival, and values above 1.0 indicate shorter survival. These results should be interpreted with caution because high heterogeneity was apparent. Future analyses in updates of this review including a larger number of studies should clarify heterogeneity for this outcome via subgroup and sensitivity analyses.

Figure 5. Forest plot of comparison: 1 Early palliative care vs TAU, outcome: 1.2 Survival.



Within the GRADE approach, we downgraded the certainty of evidence for survival to very low owing to high risk of bias at the study level across studies (-2 points due to very serious limitations in study quality: high risk of bias for selection (insufficient allocation concealment), performance, and attrition biases) and imprecision (-1 point due to imprecise data) (Summary of findings for the main comparison). We decided against downgrading for important inconsistency (large I^2) because we had already downgraded by 3 points.

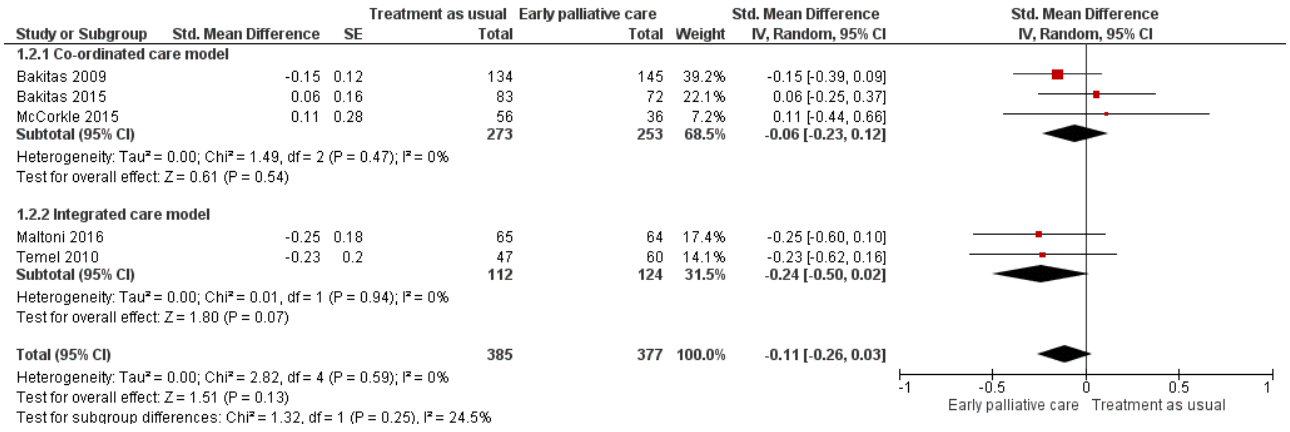
Results of individual studies

Bakitas 2009 found longer survival for the nurse-led early palliative care group than for the control group (median survival 14 months with 95% CI 10.6 to 18.4 for the intervention group vs 8.5 months with 95% CI 7.0 to 11.1 for the control group), which translates into a death HR of 0.80, with P = 0.14 favouring the early palliative care group. Bakitas 2015 also reported longer survival for the early palliative care group than for the delayed control group (median survival 18.3 months for the intervention group vs 11.8 months for the control group), which translates into a death HR of 0.64, with P = 0.03 favouring the early palliative care group. Maltoni 2016 observed a survival probability at 12 months of 38% (95% CI 28 to 48) for participants in the interventional arm and 32% (95% CI 22 to 41) for those in the standard arm. This difference was not statistically significant. Unfortunately, it was not possible to convert these data into an HR, so we did not include this study in the meta-analysis for survival. Tattersall 2014 observed median survival of 7.0 months with 95% CI 5.2 to 9.8 for the early palliative care group versus 11.7 months with 95% CI 9.8 to 18.8 for the control group. These figures translate into an HR of 1.6 with 95% CI 1.1 to 2.3 at P = 0.015, favouring the control group. Temel 2010 found longer survival for the early palliative care group (median survival 11.6 months with 95% CI 6.4 to 16.9) than for the control group (8.9 months with 95% CI 6.3 to 11.4), which translates into an adjusted HR of 0.59, with P = 0.01, or an unadjusted HR of 0.63, with P = 0.02 (unpublished data received from study authors upon request), favouring the early palliative care group.

Primary outcome: depression

Pooled data from five studies (four RCTs, one cRCT), with 762 analysed participants (sample size for available case analysis at T1) available for the relevant comparison, showed that levels of depressive symptoms for those receiving early palliative care did not differ significantly from levels for those receiving usual care (SMD -0.11, 95% CI -0.26 to 0.03) (Analysis 1.2; Figure 6). We combined different scales measuring depression across studies by applying SMDs. Positive SMDs reflect harm (more depressive symptoms), and negative SMDs indicate benefit (fewer depressive symptoms). The I^2 test detected no heterogeneity. We found that included studies used three different scales to measure depression as an outcome (Center for Epidemiological Studies - Depression Scale, CES-D, in Bakitas 2009 and Bakitas 2015; Depression subscale of the Hospital Anxiety and Depression Scale, HADS-D, in Maltoni 2016; Patient-Health Questionnaire-9, PHQ-9, in McCorkle 2015 and Temel 2010).

Figure 6. Forest plot of comparison: 1 Early palliative care vs standard oncological care, outcome: 1.2 Depression.



Within the GRADE approach, the certainty of evidence for depression was very low owing to downgrading in the light of high risk of bias at study level across studies (-2 points due to very serious limitations in study quality: high risk of bias for selection (insufficient allocation concealment), performance, detection, and reporting biases) and imprecision (-1 point due to imprecise data) (Summary of findings for the main comparison).

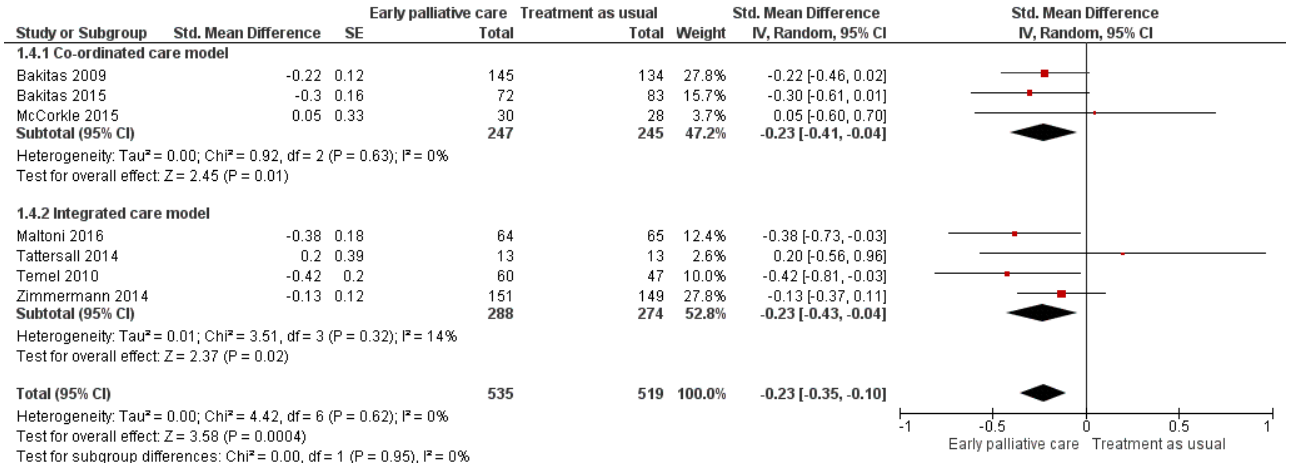
Results of individual studies

Bakitas 2009 detected lower depressed mood as measured with the CES-D for the nurse-led early palliative care group than for the control group (mean overall treatment difference of -1.8, with an SE of 0.81), which translates into an SMD or effect size of *g* = -0.15, with an SE of 0.12. At three months, Bakitas 2015 reported no significant differences between groups that again responded to the CES-D (estimated mean 11.2, with 95% CI of 9.7 to 12.7 for the early palliative group vs 10.8 with 95% CI of 9.5 to 12.1 for the delayed group), which translates into an SMD or non-significant effect size of *g* = 0.06, with a SE of 0.16. At three months, Maltoni 2016 did not find any difference in the proportion of depressed participants, as determined through the HADS-D (estimated mean 6.35 with an SD of 4.09 for the early palliative group vs 7.41 with an SD of 4.23 for the delayed group; unpublished data received upon study author request), which translates into an SMD or non-significant effect size of *g* = -0.25 with an SE of 0.18. McCorkle 2015 found no significant differences between groups that responded to the PHQ-9 (estimated mean 4.97 with an SD of 5.57 for the early palliative group vs 4.43 with an SD of 4.03 for the control group), which translates into an SMD or non-significant effect size of *g* = 0.11 with an SE of 0.28. Temel 2010 reported that participants assigned to early palliative care were significantly less depressed at three months (mean change of -0.96 with an SD of 4.65 for the early palliative group vs 0.06 with an SD of 4.07 for the standard care group), which translates into an SMD or small effect size of *g* = -0.23 with an SE of 0.2.

Primary outcome: symptom intensity

Pooled data from seven studies (five RCTs, two cRCTs), with 1054 analysed participants (sample size for available case analysis at T1) available for the relevant comparison, showed that those receiving early palliative care had significantly lower symptom intensity than those receiving usual care (SMD -0.23, 95% CI -0.35 to -0.10) (Analysis 1.4; Figure 7). The effect size was small by conventional criteria. We combined different scales measuring this outcome of interest across studies by applying SMDs. Positive SMDs reflect harm (higher symptom intensity); negative SMDs indicate benefit (lower symptom intensity). We found no heterogeneity across the included studies. We found that included studies used six different scales to measure symptom intensity as an outcome (Edmonton Symptom Assessment System, ESAS, in Bakitas 2009 and Zimmermann 2014; Quality of Life at End of Life, QUAL-E, Symptom Impact Subscale in Bakitas 2015; Hepatobiliary Cancer Subscale, HCS, of the Functional Assessment of Cancer Therapy-Hepatobiliary, FACT-Hep, in Maltoni 2016; Symptom Distress Scale, SDS, in McCorkle 2015; Rotterdam Symptom Checklist: Physical Symptoms, RSC, in Tattersall 2014; and Lung-Cancer Subscale, LCS, of the Functional Assessment of Cancer Therapy-Lung, FACT-L, in Temel 2010).

Figure 7. Forest plot of comparison: 1 Early palliative care vs standard oncological care, outcome: 1.4 Symptom intensity.



Within the GRADE approach, we downgraded the certainty of evidence for symptom intensity to low owing to high risk of bias at study level across studies (-2 points due to very serious limitations in study quality: high risk of bias for selection (insufficient allocation concealment), performance, and attrition biases) (Summary of findings for the main comparison).

Results of individual studies

Bakitas 2009 found lower symptom intensity as measured with the ESAS for the nurse-led early palliative care group than for the control group (mean overall treatment difference of -27.8 with an SE of 15), which translates into an SMD or small effect size of *g* = -0.22 with an SE of 0.12. At three months, Bakitas 2015 reported no significant differences between groups that responded to the symptom impact subscale of the QUAL-E (estimated mean 11.4 with 95% CI 10.8 to 12.1 for the early palliative group vs 12.2 with 95% CI 11.6 to 12.8 for the delayed group), which translates into an SMD or non significant effect size of *g* = -0.30 with an SE of 0.16. Maltoni 2016, applying the HCS of the FACT-Hep, detected lower symptom intensity for the early palliative care group than for the control group at three months (estimated mean 52.0 with an SD of 8.4 for the early palliative group vs 48.2 with an SD of 11.2 for the control group - here, higher scores indicate lower symptom intensity), which translates into an SMD or effect size of *g* = -0.38 with an SE of 0.18. At three months, McCorkle 2015 found no significant differences between groups that responded to the SDS (estimated mean 22.4 with an SD of 7.4 for the early palliative group vs 22.8 with an SD of 7.7 for the control group), which translates into an SMD or non-significant effect size of *g* = 0.05 with an SE of 0.33. Tattersall 2014, using the RCS, identified no significant differences

between groups at three months (estimated mean 38.0 with an SD of 9.4 for the early palliative group vs 36.0 with an SD of 9.7 for the control group), which translates into an SMD or non significant effect size of *g* = 0.2 with an SE of 0.39. Temel 2010 reported that participants assigned to early palliative care achieved significantly lower symptom intensity on the LCS of the FACT-L at three months (estimated mean 21.0 with an SD of 3.9 for the early palliative group vs 19.3 with an SD of 4.2 for the standard care group), which translates into an SMD or effect size of *g* = -0.42 with an SE of 0.2. Zimmermann 2014 found no significant differences between groups that responded to the Symptom Impact Subscale of the QUAL-E (mean difference of -0.1 with an SD of 16.9 for the early palliative group vs 2.12 with an SD of 13.9 for the control group), which translates into an SMD or non-significant small effect size of *g* = -0.13 with an SE of 0.12.

Secondary outcomes

Caregiver burden

With regard to caregiver burden, Bakitas 2009 did not observe statistically "significant main effects or interactions for time, condition or patient gender for any of the measures of caregiver burden" (N = 198; F values from 0.12 to 3.37; P = 0.07 to 0.86; unpublished detailed data received from study authors upon request). In a sample of 122 caregivers, Bakitas 2015 found a significantly better change from baseline for depression score in the early group (mean difference (MD) -3.4 on the CES-D with effect size Cohen's *d* = -0.32 and P = 0.02) (Dionne-Odom 2015). However, study authors detected no differences between groups for quality of life and burden (P = 0.39 and all P > 0.29, respectively). Caregivers of decedents had significant time-averaged between-group differences favouring the early group for depression (MD -3.8 on the CES-D with *d* = -0.39 and P = 0.02) and stress burden (MD -1.1 on the Montgomery-Borgatta Caregiver Burden Scale with *d* = -0.44 and P = 0.01) but not for quality of life (P = 0.07) or objective burden (P = 0.27) and demand burden (P = 0.22). Zimmermann 2014 noted no significant increases in the early palliative group compared (n = 77) with the control group (n = 74) for quality of life of caregivers for Caregiver QOL-Cancer, CQOL-C (P = 0.92 at three months, P = 0.51 at four months) nor the SF-36, v2 Health Survey (P = 0.83 at three months, P = 0.20 at four months) (McDonald 2016).

Healthcare utilisation

For healthcare utilisation, Bakitas 2009 did not detect statistically significant differences between groups in number of days in the hospital (P = 0.14), number of days in the intensive care unit (ICU) (P > 0.99), and number of emergency department visits (P = 0.53) after enrolment. Bakitas 2015 did not observe differences with regard to number of days in hospital (0.95 for the early palliative group vs 1.3 in the delayed group with P = 0.26), number of days in ICU (rate of use 0.1 vs 0.15 with P = 0.49), or number of emergency department visits (0.14 vs 0.16 with P = 0.21). Maltoni 2016 reported the proportion of participants who received chemotherapy in the last 30 days of life and detected a significantly lower proportion for the early palliative care than for the control group (18.7% vs 27.8% with P = 0.036; results adjusted for age, gender, marital status, and performance status). The difference in the proportion of participants who received chemotherapy during the last two weeks of life was not statistically significant (13.3% for the early palliative group vs 11.1% for the standard care group with P = 0.83). In addition, study authors found no differences of statistical significance between groups for any admission from enrolment to death (68.0% vs 73.6% with P = 0.42), any admission equal to or less than 30 days before death (50.7% vs 56.3% with P = 0.54), any emergency department visit from enrolment to death (38.7% vs 42.2% with P = 0.89), or any emergency department visit equal to or less than 30 days before death (26.7% vs 28.2% with P = 0.73). In both intervention and control groups included in Tattersall 2014, participants received an average of 1.8 lines of chemotherapy overall (1.82 lines on average for the early palliative group with SD 1.4 vs 1.81 lines on average for the control group with SD 1.5; Wilcoxon two-sample test with P = 0.92). For the subsample of participants who had died at follow-up (N = 105), Temel 2010 showed that a greater percentage of participants in the control group than in the early palliative care group had received "aggressive end-of-life care", that is, chemotherapy within 14 days before death, no hospice care, or admission to hospice three days or less before death (54% vs 33% at P = 0.05), and fewer participants in the control group than in the early palliative care group had resuscitation preferences documented (28% vs 53% at P = 0.05). No statistically significant differences were found for the overall number of chemotherapy regimens, rates of admission, number of emergency department visits, or median duration of hospice care. Zimmermann 2014 found no differences between groups in the proportion of participants receiving chemotherapy (86% in the intervention group vs 89% in the control group with P = 0.36) and in the proportion receiving radiation (21% vs 15% with P = 0.14).

Harms/adverse events

With regards to harms/adverse events, Tattersall 2014 measured a higher percentage of participants in the early group with severe scores for pain and poor appetite along with a higher level of unmet needs. All other studies did not publish data on adverse events. On request, the principal investigators of the Bakitas 2009, Bakitas 2015, Maltoni 2016, McCorkle 2015, Temel 2010, and Zimmermann 2014 trials stated that they had not observed any harms/adverse events during their study (e-mail correspondence on 21 May 21, 4 and 5 November, 2016).

Other reported outcomes, not prespecified in the protocol

Place of death

Bakitas 2015 considered place of death and reported no differences in the percentage of participants who died at home (54% in the early palliative care group vs 47% in the control group at P = 0.60). This was consistent with results from Tattersall 2014, which found no differences in place of death between groups (P = 0.46). In Temel 2010, investigators observed no differences between groups in the percentage of participants who died at home (84% in the intervention group vs 70% in the control group at P = 0.10). Maltoni 2016 reported no significant differences between early palliative and control groups in the proportion of participants dying at home or in hospice (77.8% vs 66.7% with P = 0.14).

Problems with medical interactions and satisfaction with care

Zimmermann 2014 investigated participants' problems with medical interactions (using the Cancer Rehabilitation Evaluation System Medical Interaction Subscale, CARES-MIS) as a secondary outcome but did not identify differences between groups. In contrast, researchers found significant differences in participants' satisfaction with care (with FAMCARE-P19) (mean change score 2.33 with SD of 9.10 for the intervention group, mean change score -1.75 with SD of 8.21 for the control group; P = 0.0003). For caregivers,

Zimmermann 2014 observed improved satisfaction with care in the early palliative care group compared with the control group at three months (mean change from baseline 1.4 with 95% CI -1.2 to 4.1 vs mean change from baseline -3.1 with 95% CI -6.6 to 0.3; P = 0.007) and at four months (mean change from baseline 0.6 with 95% CI -2.6 to 3.8 vs mean change from baseline -2.4 with 95% CI -5.1 to 0.2; P = 0.02) (McDonald 2016). Maltoni 2016 reported no differences between groups in their trial with respect to level of family satisfaction with care, as assessed with FAMCARE-20 (estimated mean 33.3 with an SD of 8.4 for the early palliative group vs 33.8 with an SD of 7.5 for the control group), which translates into an SMD or non-significant effect size of *g* = -0.06 with an SE of 0.18.

Illness and prognosis understanding

With respect to illness and prognosis understanding, results from Temel 2010 indicate that a "greater percentage of patients assigned to early palliative care retained or developed an accurate assessment of their prognosis over time (82.5% versus 59.6%; P value = 0.02) compared with those receiving standard care", and that participants "receiving early palliative care who reported an accurate perception of their prognosis were less likely to receive intravenous chemotherapy near the end of life (9.4% versus 50%; P value = .02)".

Between-study subgroup analysis for models of early palliative care

Subgroup analyses are in their nature entirely observational and may include potential bias through confounding by other study-level characteristics. Nevertheless, as prespecified in the analysis plan in the protocol, we compared studies following the co-ordinated care model against those based on an integrated care model for health-related quality of life, depression, and symptom intensity (Figure 4; Figure 5; Figure 6). We decided against a subgroup analysis for survival, as one (Tattersall 2014) of the two studies (Tattersall 2014; Temel 2010) in the potential integrated care subgroup is an outlier study. With respect to health-related quality of life, the magnitude of the difference was practically unimportant (SMD 0.21, 95% CI 0.03 to 0.39, for the co-ordinated care model; SMD 0.29, 95% CI 0.14 to 0.44, for the integrated care model). The test for subgroup differences indicated that the difference was not statistically significant (P = 0.51). We made similar observations for differences in depression (SMD -0.06, 95% CI -0.23 to 0.12 for the co-ordinated care model; SMD -0.24, 95% CI -0.15 to 0.02, for the integrated care model) and symptom intensity, respectively (SMD -0.23, 95% CI -0.41 to -0.04, for the co-ordinated care model; SMD -0.19, 95% CI -0.43 to 0.06, for the integrated care model). Tests for subgroup differences indicated that the differences were not statistically significant (P = 0.25 and P = 0.80, respectively).

Between-study sensitivity analysis for study design (RCT vs cRCT)

For the sensitivity analysis for study design (RCT vs cRCT), we excluded the two cRCTs (McCorkle 2015; Zimmermann 2014) and pooled results from the five "pure" RCTs for both health-related quality of life and symptom intensity (Bakitas 2009; Bakitas 2015; Maltoni 2016; Tattersall 2014; Temel 2010). For quality of life, the overall effect was only marginally greater and small (SMD 0.29, 95% CI 0.14 to 0.44), and studies showed no significant heterogeneity (Figure 8). For symptom intensity, the overall effect was somewhat greater but still small (SMD -0.28, 95% CI -0.43 to -0.13), and again studies showed no significant heterogeneity (Figure 9). We did not include a cRCT for the survival outcome. For depression, we included only a single cRCT in the corresponding meta-analysis. Hence, we did not conduct a sensitivity analysis for these two outcomes.

Figure 8. Forest plot of comparison: 1 Early palliative care vs standard oncological care, outcome: 1.5 Health-related quality of life (sensitivity analysis for study design including RCTs only).

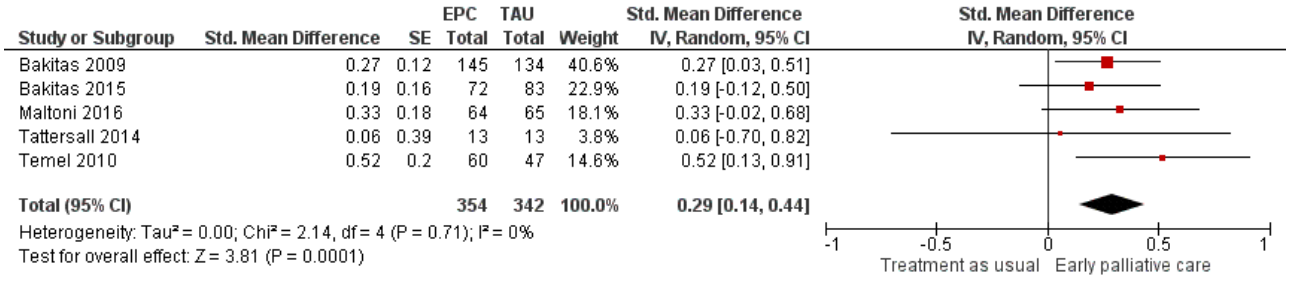
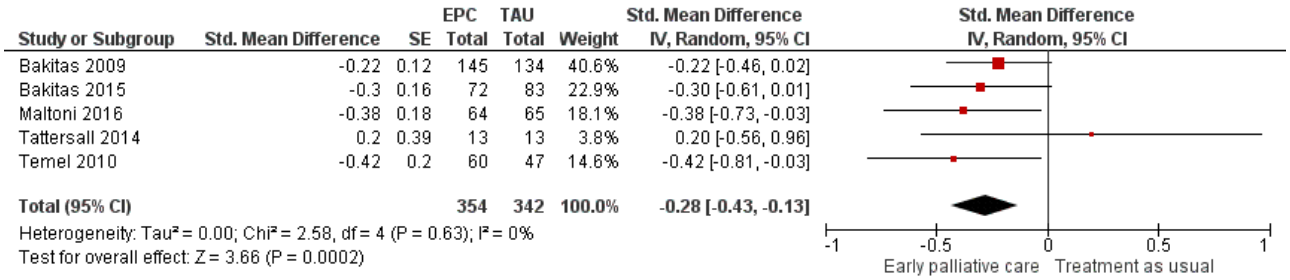


Figure 9. Forest plot of comparison: 1 Early palliative care vs standard oncological care, outcome: 1.6 Symptom intensity (sensitivity analysis for study design including RCTs only).



DISCUSSION

Summary of main results

First studies on the efficacy of early palliative care in patients with a diagnosis of metastatic disease and limited prognosis have yielded evidence of low certainty indicating benefit for health-related quality of life. Meta-analyses of seven studies analysing 1028 participants with respect to quality of life and 1054 participants with respect to symptom intensity showed that early palliative care improves quality of life on average by 0.27 standardised mean deviations over usual care controls. In addition, early palliative care decreases symptom intensity by on average 0.23 standardised mean deviations over controls. By conventional criteria, these effects are considered small. Certainty of the evidence for quality of life and symptom intensity was low. In additional meta-analyses, we found no significant differences between groups for survival or decreased depression. However, we found evidence of very low certainty for effect estimates of these two outcomes. Evidence on healthcare utilisation remains inconclusive and only two studies have reported positive findings. We found results favouring early palliative care with regard to satisfaction with care and illness and prognosis understanding. However, for each of these two outcomes, only two studies and a single study, respectively, provided evidence. One of the two studies on satisfaction with care reported no differences between groups. With respect to models for delivery of early palliative care, we noted no practically relevant differences between the co-ordinated care model and the integrated care model.

Overall completeness and applicability of evidence

Our highly sensitive electronic search combined with further intensive efforts to locate grey literature and unpublished studies yielded an enormous amount of information to be evaluated. In this regard, interrater agreement for inclusion was good. We therefore believe that we have found the complete evidence on early palliative care so far available. We were able to identify several randomised controlled trials (RCTs), allowing for pooling of the best available evidence on different outcomes. However, with only seven studies included in the meta-analyses, it would be premature to state that current evidence is fully comprehensive. This especially accounts for some process-related outcomes such as communication of prognosis and economic evaluation, which have not yet been investigated extensively. The large number of RCTs that are ongoing or completed but awaiting assessment (e.g. Temel 2017; Van Arsdale 2016), as well as manifold additional non-controlled evaluation studies (e.g. May 2015; Meffert 2015) demonstrate that early palliative care is a field of high interest that is still under development. Moreover, most studies were conducted in tertiary referral hospitals that rely on highly specialised palliative care services. Furthermore, most of the included studies were run in North America and Australia, and specialised palliative care services were often established for quite some time before study initiation. From an international perspective, we are aware that the current practice of oncology and palliative care certainly varies to a large degree (Luckett 2014), and that health policies and resources (e.g. workforce challenges) differ between countries (Gaertner 2015; Hui 2015a; Janssens 2016). This also applies to the included studies, as the seven studies that analysed "experimental settings" varied substantially, and interventional models were somewhat heterogeneous. In sum, applicability of results with respect to the broader range of healthcare services is limited at present. Thus, we would recommend that future studies should specify explicitly both the respective early palliative care intervention under investigation and the standard care condition. Only then will early palliative care be validated through rigorously conducted (cluster-)randomised studies drawing on well-defined patient populations and settings. Notwithstanding, early palliative care has also been investigated in non-oncological conditions with progressive decline and ultimately limited prognosis (e.g. chronic obstructive pulmonary disease (COPD), Weber 2014; human immunodeficiency virus (HIV), Lofgren 2015; and end-stage liver disease, Baumann 2015).

To put results for effect estimates back into the clinical context, the mean health-related quality of life score for patients given early palliative care was on average approximately 4.59 (95% confidence interval (CI) 2.55 to 6.46) points higher on the Functional Assessment of Cancer Therapy-General (FACT-G), assuming a standard deviation (SD) of 17.0 in a sample of patients with advanced cancer (Brucker 2005). This is close to the minimal clinically important difference of 5 points on the 0 to 108 FACT-G scale (Brucker 2005). For symptom intensity, effect estimates correspond to an average reduction of approximately -35.4 (95% CI -53.9 to -15.4) points on the Edmonton Symptom Assessment Scale (ESAS) scale, assuming an SD of 154 in a sample of patients with advanced cancer (Bakitas 2009). To the best of our knowledge, no minimal clinically important difference has been defined for overall ESAS score. However, more recently, 8 to 22 points was determined as the minimal clinically important difference for improvement on each of the ESAS symptoms in a sample of patients with cancer, most of whom had metastatic disease (Hui 2015c).

Quality of the evidence

For health-related quality of life, Temel 2010 reported the largest effect size for early palliative care. The explanation may lie in the

particularly high "dose" of palliative care and the high disease severity of the study population, which consisted solely of patients diagnosed with metastatic non-small lung cancer. For health-related quality of life, survival, and symptom intensity, Tattersall 2014 emerged as an outlier, indicating an effect in a different direction when compared with all other included studies. However, as already stated, for this study, we identified high risk for attrition bias (alongside performance bias). Results of this study are likely to account for the modest dispersion in effects seen for three of the four selected primary outcomes of our review. However, given the current state of the literature, we cannot completely determine the reason for dispersion in effects. Possible explanations may include that dispersion is a result of bias at the study level, that is, results on adverse events have to be interpreted against the background of baseline imbalance between groups favouring the control group, as well as an exceptionally high attrition rate across groups in comparison with the other included studies, or dispersion may be due to plausible but yet to be detected study-level covariates. Tattersall 2014 discussed differences in eligibility (heterogeneous cancer types), lower 'doses' (number of contacts between participant and palliative care team), and a less comprehensive framework for the intervention compared with other trials (Bakitas 2009; Temel 2010) as possible explanations.

With respect to risk of bias at the study level, we did detect evidence for selection bias for two trials (Temel 2010; Zimmermann 2014). We found high risk of performance bias (i.e. blinding of participants) in six of the seven included studies (Bakitas 2009; Bakitas 2015; Maltoni 2016; McCorkle 2015; Tattersall 2014; Temel 2010). For blinding of outcome assessment, we did not find necessary information in publications for five of the seven included studies (Bakitas 2009; Maltoni 2016; McCorkle 2015; Tattersall 2014; Temel 2010); one study stated that assessors were blinded (Bakitas 2015), and one that they were not (Zimmermann 2014). Apart from these two studies, risk of bias for this domain remained unclear. We identified high risk of attrition bias for Tattersall 2014 and made a close-call decision for low risk of selective reporting bias in Bakitas 2015 (study authors did not differentiate between primary and secondary outcomes but reported all key outcomes). All in all, with respect to the subsequent rating of certainty of the evidence at the outcome level, these findings implied very serious study limitations (high risk of bias at the study level) for all outcomes. In any case, we would like to underscore that particularly blinding of participants often constitutes a major challenge for studies on complex interventions in general, and on palliative care in particular. In light of these field-specific conditions, several included studies still can be considered of high quality, given the ecological context of complex interventions (Movsisyan 2016b).

At the outcome level, with regard to certainty of effect estimates measured according to GRADE, certainty of findings ranked from very low to low across different outcomes. Specifically, indirectness was a concern, as two studies were conducted exclusively in patients with metastatic pancreatic and advanced lung cancer, respectively (Maltoni 2016; Temel 2010), and all studies exhibited substantial differences in intervention models and control conditions. Nonetheless, we saw no need to downgrade for indirectness, as it is usually unnecessary for the intended populations and interventions to be identical. Interventions are usually delivered in different settings, and we did not assume that "the biology in the population of interest is so different [from] that of the population tested that the magnitude of effect will differ substantially" (Guyatt 2011b). In addition, we found high inconsistency for survival. This observation may be linked mainly to the fact that study populations varied across studies, and that investigators used a range of interventional models. Also, small effects could have resulted from a scarce difference between experimental and control conditions within the individual study (e.g. in the Maltoni 2016 trial, in which routine care was carried out by oncologists with profound expertise in symptom management and palliative care). Uncertainty of findings is almost certainly a result of the small number of studies completed in this newly emerging field, in which many studies are ongoing or have been initiated only recently. Even across the few completed studies, included outcomes varied to a fair degree, for example, depression and survival were not regarded as relevant in all studies. A major reason for downgrading across different outcomes was imprecision with regard to the pooled effect size and high risk of bias at the study level. Research in the field of early palliative care is just emerging, with the first large RCTs published only recently. Inclusion of only a few studies in this review impeded examination of a priori hypotheses about possible effect modifiers. At this point, we argue that current certainty of the evidence for crucial primary outcomes demands that results are interpreted with caution owing to low certainty of current evidence, especially as time points for post-interventional outcome assessment also vary across studies. However, future findings from current ongoing studies may strengthen the certainty of effect estimates and may further clarify the problem of applicability of early palliative care. Owing to the large number of studies currently under way and yet to report, we would expect that more evidence will become available regarding effects of the early palliative care intervention and that this evidence will be of higher certainty; which populations will find early palliative care to be specifically effective; and whether a specific model of early palliative care is more effective.

Potential biases in the review process

As is common in meta-analysis, the appropriateness of combining results across studies is based on a fair amount of subjectivity and is usually worthy of discussion. At the very least, meta-analysis provides clear descriptions and transparency. Our explicit intent was to gain a broader perspective on the evidence for early palliative care, which is a complex intervention by its nature. In the light of sufficiently homogeneous outcome constructs, measures of which were combined by applying standardised mean differences (SMDs), we decided to synthesize pooled effect sizes on the outcome level. We claim that we arrived at a meaningful summary but underscore that evidence for most outcomes lacks adequate robustness at this point. In accordance with the GRADE approach, we went for an outcome-specific certainty of effect estimates rating. Empirical evidence supporting these criteria is limited, and attempts to show systematic differences between studies that meet and do not meet the specific criteria have yielded inconsistent results (Guyatt 2011a). Furthermore, the relative weight that one should put on these criteria remains uncertain. However, we agree with the GRADE Working Group in underscoring that the approach does not primarily ensure consistency of conclusions but delivers explicit and transparent judgements for systematic reviews (Guyatt 2011a). Focussing on the description of the certainty of effect estimates rather than on direct provision of clinical guidance, we have presented certainty ratings for each outcome and have not determined the certainty of effect estimates across outcomes. However, it has been that the lowest certainty rating of critical

outcomes should be applied as the overall certainty associated with a recommendation (Guyatt 2013). Consistent with this argument, one would have to regard current certainty of the evidence for early palliative care as very low, with the lowest certainty rating assigned for the crucial outcome of survival. However, because this rating is likely to be based on bias at the study level, we would refrain from adopting such a pessimistic view on early palliative care, that is to say, we are in need of larger studies to establish robustness with regard to effect estimates.

One major strength for prevention of bias within the review process itself is the best possible control for publication bias. Otherwise, synthesis of a biased sample emerges that neglects unpublished findings systematically differing from results of the included studies. As mandatory registration of RCTs may be the only reliable method of addressing publication bias, and as this is becoming increasingly common, we undertook an extensive search in clinical trial registers and incorporated findings into our synthesis to assess the risk of publication bias and further look into potential selective reporting (Guyatt 2011a). Therefore, we compared the sample of the seven included studies with results from searches of grey literature and trial registers for systematic differences. In doing so, we identified no unpublished studies, apart from those that are still ongoing. Drawing on a comprehensive literature search with assistance from the PaPaS Group, we were able to minimise availability, familiarity, and citation bias for records more difficult to detect. We therefore assume that our synthesis is based on an unbiased sample that is fairly representative of the target population. However, especially given that research on early palliative care is a newly emerging field, we cannot completely rule out time-lag bias, that is, longer delay to publication for non-significant studies. Time-lag bias would lead to overestimation of true effect sizes. In the future, tests examining whether evidence changes over time could further control for publication bias. For example, within the recursive cumulative meta-analysis approach, a meta-analysis performed at the end of each year for studies ordered chronologically notes changes in the summary effect (Borenstein 2009).

Concerning eligibility criteria, we decided that for inclusion, estimates of participants' survival had to be two years or less, and that participants with predicted survival of less than three months at study inclusion had to be excluded. This criterion was a necessary consequence of applying the time-based model for indication of early palliative care. We are well aware that this strategy entails some arbitrary decisions that need profound elaboration in the ongoing debate on early palliative care. Remarkably, we found a fair amount of variation in eligibility criteria and consequently in the number of included studies across the most recent systematic reviews published before this meta-analysis was completed. We agree with Simone 2nd 2015 that "the definition itself of early palliative care is not without considerable confusion" - a problem that has also been stated as unresolved in one of the latest systematic reviews on early palliative care (Davis 2015). However, from a pragmatic point of view, we consider this conceptualisation appropriate for arriving at an initial overview on the evidence for early palliative care, and we reached a good degree of interrater agreement.

Agreements and disagreements with other studies or reviews

We identified 10 narrative or systematic reviews published before this review, which dealt specifically with early palliative care (Bauman 2014; Davis 2015; Greer 2013; Hui 2015b; Parikh 2013; Salins 2016; Smith 2012; Tassinari 2016; Zambrano 2016; Zhi 2015); however, none of these reviews included all of the randomised trials included in the current review. To our knowledge, this Cochrane review provides both the first systematic assessment of study quality and evidence certainty and the first meta-analyses on early palliative care.

Two early narrative reviews on this topic by Greer 2013 and Bauman 2014 discussed two or three of the first studies that we also included and concluded that these trials “demonstrate that early integration of palliative care improves quality of life, depression, prognostic understanding, and health service use in patients with advanced cancer” and "possibly prolong survival (i.e. in the case of those with metastatic NSCLC." Parikh 2013 mentioned the Bakitas 2009, Temel 2010, and Zimmermann 2014 trials and drew similar conclusions, emphasising that “early provision of specialty palliative care [...] lowers spending", and that "more evidence is needed to show the potential gains of early palliative care in other populations”.

The American Society of Clinical Oncology Provisional Clinical Opinion on the Integration of Palliative Care into Standard Oncology Care (Smith 2012) was based on seven RCTs and did not state a survival benefit from early palliative care but described an associated “improvement in symptoms, QOL, and patient satisfaction, with reduced caregiver burden”, along with “more appropriate referral to and use of hospice, and reduced use of futile intensive care”.

In two of the latest narrative reviews, Davis 2015 and Zhi 2015 reported effects in accordance with our findings. However, they underscored that published randomised trials do not demonstrate benefits for symptom intensity and quality of life, and that resource utilisation and costs often do not differ from standard care.

In the most recent systematic reviews covering RCTs, systematic reviews, surveys, observational studies, and qualitative studies (Salins 2016; Tassinari 2016; Zambrano 2016), study authors concluded that "in terms of outcomes and quality indicators for care in the last days of life, evidence is still lacking".

Of note, none of the reviews mentioned above reported or even cited the Tattersall 2014 study. All in all, the first narrative reviews tended to state clear superiority for early palliative care for a wide range of outcomes. With emerging evidence, reviews provided a more critical appraisal, especially regarding superiority of early palliative care for survival. This Cochrane review is the first to conduct a meta-analysis and to evaluate the certainty of evidence. Findings indicate small effects at most along with evidence of very low to low certainty across outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

All stakeholders shall be advised that besides the seven included studies, we identified 20 ongoing studies and 10 studies awaiting assessment. Therefore, the evidence base for early palliative care in cancer is growing, and conclusions remain preliminary.

For people with advanced cancers

Available evidence of very low to low certainty suggests that patients with advanced cancers could benefit from early palliative care with respect to small improvements in quality of life and symptom intensity. At this point, effects on survival and/or on depressive symptoms remain uncertain. Nevertheless, to improve quality of life and reduce symptoms, patients could approach their attending physician and request referral to palliative care at an early stage of disease.

For clinicians

From a practitioner's perspective, some previous reviews have reported definitive success of early palliative care interventions for improving quality of life, controlling bodily symptoms and depressive symptoms, and prolonging life. However, according to our results, these claims were likely to be at least premature for the entire group of patients with advanced cancer. Besides studies favouring such outcomes, we also detected a study with possibly negative effects on symptoms and survival. More research is needed before solid conclusions regarding routine care can be drawn. Included studies were heterogeneous in many aspects. Although we found some possibly clinically relevant evidence for the effectiveness of early palliative care in terms of quality of life and symptom intensity, the certainty of this evidence was low to very low. Results of our review do not support that early palliative care leads to prolonged survival in general. Therefore, at this point, clinicians could consider early palliative interventions on a case-by-case basis to address quality of life alongside symptom intensity and counsel patients adequately (Peppercorn 2011), but refrain from claiming that these interventions will have an additional impact on survival, or that they offer the only way to target quality of life. The patient should be informed adequately and his or her wishes should be respected during treatment planning.

For policy makers

Access to additional specialised palliative care teams is currently limited and availability of services is often absent even in developed countries (Kelley 2015). Hence, policy makers face the challenge of systematically introducing early palliative care into environments with potentially limited available resources. At this point, we have found no evidence that specialised palliative care teams (as part of integrated care) are superior to those providing a generic palliative care approach (co-ordinated care). In addition, cost utility of early palliative care remains unclear at this point. However, findings of our review do support strong implementation of elements of early palliative care in clinical routines. These elements may consist of advanced communication for identification of patient priorities, care co-ordination towards symptom control, and comprehensive psychosocial care potentially involving caregivers (Janssens 2016).

Implications for research

General

With only seven studies included, we clearly need additional sufficiently powered and well-designed studies. Especially with respect to effect estimates of outcomes other than health-related quality of life and symptom intensity, we are in need of larger (i.e. multi-centred) studies to establish robust evidence. Besides uniform and significant effects, we found that studies differed in average effect size or even in the direction of effects. To explain this heterogeneity with respect to entity, interventions, dose, and study methods further, we need to continue to work on an even clearer, evidence-based definition for early palliative care (Lee 2015). A clearer definition would constitute the foundation for establishing and comparing interventions across studies, and first efforts would stem from qualitative studies on core interventional elements (Hui 2015a; Jacobsen 2011; Janssens 2015; Yoong 2013). In general, we consider it essential to better describe training as well as therapist adherence. It is equally important to provide more information on the usual care provided locally. To ensure clear interpretation of findings, we should provide a thorough and extensive description of both experimental and control conditions.

Against the background of evidence presented here, it has to be considered that early palliative care in cancer is still a relatively new treatment approach that has so far almost exclusively been evaluated in the context of tertiary care contexts; and is not a clearly defined and homogeneous type of intervention; but that research is important because early palliative care may have the potential to improve current clinical practice in advanced cancer diseases.

Design

Interventions should be described under the different models proposed for early palliative care, and frequency and duration of treatment should be stated. For strengthening the internal validity of effect estimates, future studies need to be rigorous in both design (ideally controlling for palliative care skills/training of oncologists/palliative care physicians and high- vs low-volume centres) and delivery, and should be based on sufficient power. Specifically, investigators in future studies should use all available measures to control for selection bias (i.e. to ensure adequate allocation concealment), performance bias (i.e. to blind study participants), detection bias (i.e. to blind outcome assessors), and selective reporting (i.e. to report studies as indicated in the preregistration). It is most important that investigators provide detailed descriptions of the several components of both intervention and control conditions. Notwithstanding, for ethical and disease-inherent reasons, conducting RCTs and restricting attrition are major challenges in palliative care (Wee 2008). With respect to setting, interventions should be expanded beyond high-volume tertiary referral hospitals in Western countries. It has been shown that clinical expertise and centre volume impact treatment effect (Choudhry 2005). Specifically, treatment in comprehensive cancer centres is often linked with superior survival (Wolfson 2015). Although research on the transferability of early palliative care interventions to more naturalistic contexts has already commenced, we would encourage investigators to focus first on rigorous RCTs that follow conventional designs to determine internal validity, substantiate findings, and increase the certainty of evidence. Concerning homogeneity of samples, it might be worthwhile to investigate 'tumour homogeneous' samples to better account for specific disease trajectories and patient characteristics (e.g. male gender and young age in patients with lung cancer, as recently demonstrated by Nipp 2016) that are likely to specifically impact the effectiveness of an early palliative care approach. Only in a second step, that is, when certainty of effect estimates is higher, may pragmatic studies looking at implementability of early palliative care be initiated (Treweek 2009). *If* early palliative care proves effective in the future, we regard continuation of studies along this pragmatic-explanatory continuum as crucial (Loudon 2015; Thorpe 2009).

Measurement (endpoints)

Concerning measurements, health-related quality of life and symptom intensity have emerged as appropriate outcomes that are possibly sensitive to change and can be recommended for routine collection. In addition, affective symptoms should be assessed, as they constitute a particular salient distress factor in patients with advanced cancer (Haun 2014; Mehnert 2014). Compared with these endpoints, survival is controversial, as it is not the primary aim of palliative interventions. However, in terms of further advancements, information on how the intervention may work and on essential components should be derived. Moreover, future studies need to harmonise measurements with respect to applied scales and predefined time points. The most common follow-up for primary outcomes currently occurs at 12 weeks. Blinding of outcome assessment is essential, as is its explicit reporting in publications.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bakitas 2009

Methods	Parallel-group randomised controlled trial (RCT)
Participants	**Country and regions:** USA, rural area; Norris Cotton Cancer Center (NCCC) and Dartmouth College in Lebanon, New Hampshire, and affiliated outreach clinics, Veterans Administration Medical Center (VAMC), in White River Junction, Vermont **Recruitment:** identification by research assistants at NCCC and VAMC tumour boards (gastrointestinal, genitourinary, breast, and thoracic cancer management meetings) and review of clinicians' clinic schedules **Inclusion criteria:** 18 years of age or older; life-limiting cancer (prognosis approximately 1 year); and within 8 to 12 weeks of a new diagnosis of gastrointestinal tract (unresectable stage III or IV), lung (stage IIIB or IV non–small cell or extensive small cell), genitourinary tract (stage IV, prostate cancers limited to persons with hormone refractory), or breast (stage IV and visceral crisis, lung or liver metastasis, oestrogen receptor (ER) negative, human epidermal growth factor receptor 2 (Her 2 neu) positive)) cancer **Exclusion criteria:** impaired cognition (< 17 on the Adult Lifestyles and Function Interview-Mini Mental State Exam); and Axis I psychiatric disorder (schizophrenia, bipolar disorder) or active substance use disorder **Number of participants enrolled (survival outcomes sample):** N = 322 (161 intervention and 161 control) randomised **Participant characteristics (patient outcomes sample):** N = 279 (87% returned baseline questionnaires); mean age (intervention/control in years): 65.4/65.2; male gender (intervention/control in %): 62.1/58.2; married or living with partner (intervention/control in %): 73.1/67.2; education < 9 years (intervention/control in %): 11.7/14.9; Caucasian (intervention/control in %): 98.6/98.5; employed (intervention/control in %): 20.0/16.4; live in rural setting (intervention/control in %): 52.4/60.5; Karnofsky Performance Status (intervention/control mean): 78.4/77.4; differences between intervention and control not statistically significant **Diseases (patient outcomes sample, intervention/control in %):** gastrointestinal tract cancer 42.1/43.3; lung cancer 34.5/32.1; genitourinary 13.1/13.4; breast 10.3/11.2; differences between intervention and control not statistically significant **Deaths at end of study (intervention/control in N (%)):** 112 (69.6)/119 (73.9); differences between intervention and control not statistically significant **Withdrawals/other drop-outs (intervention/control in N (%)):** 16 (9.9)/27 (16.8); differences between intervention and control not statistically significant (P = 0.10) **Number of caregivers enrolled (intervention/control in N):** 116/104 **Caregiver characteristics (caregiver outcomes sample):** mean age 59.0 years; male 22.7%; married or living with partner 83.3%; education < 9 years 6.1%; Caucasian 96.5%; employed 42.9%; relationship to patient: spouse/partner 70.7%, child 16.2%
Interventions	**Name:** educational and care management palliative care intervention for persons with advanced cancer and a caregiver compared with care as usual (project ENABLE II) **Service base:** outpatient palliative care **Intervention condition (n = 161):** case management and educational approach with a manualised, telephone-based format carried out by 2 advanced practice nurses with palliative care specialty training; 4 initial structured educational and problem-solving telephone sessions on a weekly basis (education manual: *Charting your Course: An Intervention for People and Families Living With Cancer*) and at least monthly telephone follow-up sessions thereafter until the participant died or the study ended; problem-solving management on the basis of systematic distress assessment using the Distress Thermometer with a cut-off > 3; when concerns were identified, participants were encouraged to contact

Bakitas 2009 *(Continued)*

	the oncology or palliative care clinical teams; monthly medical appointments for participants and their caregivers (attendance in person or by toll-free conference call) led by a palliative care physician and nurse practitioner, biweekly study team meetings to review audiotaped educational sessions with regards to difficult patient management issues **Control condition (n = 161):** free access to all oncology and supportive services without restrictions, including referral to the institution's interdisciplinary palliative care service for symptom and supportive care, free access to an advanced illness co-ordinated care program (Advanced Illness Care Committee, AICC) that provided consultation to oncology staff for inpatients with life-limiting illness at the VAMC (including prognosis and goals of care assessment, pain and symptom management, advance care planning, referral to hospice)
Outcomes	**Primary endpoints:** patient-reported quality of life (Functional Assessment of Chronic Illness Therapy-Palliative Care, FACIT-Pal), symptom intensity (Edmonton Symptom Assessment Scale, ESAS), and resource use (number of days in the hospital, number of days in intensive care unit, and number of emergency department visits) **Secondary endpoints:** mood status (Center for Epidemiological Studies-Depression scale, CES-D), survival, caregiver burden (Montgomery Borgatta Caregiver Burden Scale), quality of care (After Death Bereaved Family Member Interview, ADI) **Assessment points:** baseline/T0: after randomisation; T1: 1 month after baseline; then every 3 months until the participant died or the study was completed (31 December 2007)
Notes	**Funding source:** National Cancer Institute (NCI), USA **Declarations of interest among primary researchers:** no financial disclosures reported. Dr Bakitas was a recipient of a Department of Defense Clinical Nurse Researcher award, an American Cancer Society Doctoral scholarship, and a postdoctoral fellowship at Yale University School of Nursing (National Institutes of Health/National Institute of Nursing Research grant T32NR008346). This study was supported by National Cancer Institute grant R01 CA101704 **Power considerations:** At study completion, final enrolment was 322 owing to slower accrual than was projected in the initial power calculation (target sample size of 400, 80% power for scores on FACIT-Pal, ESAS, and CES-D based on a *t* test comparing treatment groups with respect to the last observed value at a 2-sided alpha of .01). Reduced sample size and power might have increased the probability of type II error

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from main publication: "Participants were randomised equally into either the intervention or the usual care group using computer-generated random numbers" Judgement: probably done, as investigators consistently describe the use of random sequences
Allocation concealment (selection bias)	High risk	Quote from main publication: "Referring clinicians were neither informed nor formally blinded to participant assignment" Judgement: probably not done
Blinding of participants (performance bias)	High risk	Preregistration on clinicaltrials.gov (NCT00253383); says it was an open-label trial Judgement: not done
Blinding of outcome assessment (detection bias)	Unclear risk	Original publication does not explicitly address blinding of outcome assessment

Bakitas 2009 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement: N = 113 completers in intervention group vs N = 105 completers in control group (Fisher's exact test with 2-tailed P = 0.40)
Selective reporting (reporting bias)	Low risk	Judgement: All outcomes from clinicaltrials.gov registration listed and reported in publications
Other bias	Low risk	None detected

Bakitas 2015

Methods	Parallel-group randomised controlled trial (RCT) with fast-track/delayed-intervention design
Participants	**Country and regions:** USA, Norris Cotton Cancer Center and Dartmouth College in Lebanon, New Hampshire, Veterans Administration (VA) medical centre in White River Junction, Vermont **Recruitment:** 29 months, identification by research assistants/research co-ordinators reviewing all outpatient clinicians' schedules and tumour board lists **Inclusion criteria:** able to speak and understand English; over the age of 18; new diagnosis, recurrence, or progression of advanced stage cancer within approximately 60 days of the date the patient was informed of the diagnosis by his/her oncology clinician; estimated survival of 2 years or less; diagnosed advanced stage solid tumour such as one of the following: • lung cancer: stage IIIB or IV non-small cell, or extensive stage small cell • breast cancer: stage IV with poor prognostic indicators including but not limited to > 2 cytotoxic regimens for metastatic breast cancer (MBC) or diagnosis of MBC ≤ 12 months since completion of adjuvant or neo-adjuvant treatment, or triple negative disease (ER/PR and HER-) or parenchymal brain mets and/or carcinomatous meningitis gastrointestinal cancers: unresectable stage III or IV • genitourinary cancers: stage IV (for prostate cancer inclusion is limited to persons with hormone refractory prostate cancer) • brain cancer: unresectable; grade IV • melanoma: stage IV • haematological malignancies: leukaemia (e.g. acute myeloid leukaemia, acute lymphoblastic leukaemia, chronic myeloid leukaemia, chronic lymphoblastic leukaemia) with advanced stage, treatment refractory, poor prognosis cell type or chromosomal abnormalities, "older age"; lymphoma with stage IV, treatment-refractory Hodgkin's disease or non-Hodgkin's lymphoma; multiple myeloma with elevated β_2-microglobulin, albumin < 3.5 g/dL, plasma cell labelling index > 1%, CRP > 6 µg/mL, elevated lactate dehydrogenase, plasmablastic morphology, abnormal chromosome 13 **Exclusion criteria:** dementia or significant confusion (impaired cognitive status as indicated by a score ≤ 3 on the Callahan 6-item cognitive screening tool); Axis I psychiatric diagnosis of severe mental illness (DSM-IV) (e.g. schizophrenia, bipolar disorder, active substance use disorder); patients were not excluded if they had not identified a caregiver; 4. prior involvement with palliative care service within the past year; minimum predicted survival < 12 weeks (3 months) **Number of participants enrolled:** N = 207 (104 intervention and 103 control) randomised **Patient characteristics:** N = 207; mean age (intervention/control in years): 64.0/64.6; male gender (intervention/control in %): 53.9/51.5; married or living with partner (intervention/control in %): 73.1/69.7; education < 9 years (intervention/control in %): 7.7/2.9; Caucasian (intervention/control in

Bakitas 2015 *(Continued)*

	%): 98.1/95.2; employed (intervention/control in %): 24.0/23.3; live in rural setting (intervention/control in %): 59.6/58.3; Karnofsky Performance Status (intervention/control mean): 80.6/81.5; intervention group with significantly less education, higher weekly alcoholic beverage use, and higher clinical trial enrolment **Diseases (intervention/control in %):** lung cancer 44.2/40.8; gastrointestinal tract 25.0/23.3; breast 9.6/12.6; other solid tumour 9.6/9.7; genitourinary tract 6.7/8.7; haematological malignancy 4.5/4.6; differences between intervention and control not statistically significant **Deaths at end of study (intervention/control in N (%)):** 50 (48.1)/59 (57.3); difference between intervention and control not statistically significant **Withdrawals/other drop-outs (intervention/control in N(%)):** 12 (11.5)/22 (21.4); difference between intervention and control not statistically significant (P = 0.06) **Number of caregivers enrolled (intervention/control in N):** 63/61 **Caregiver characteristics (intervention/control in N (%)):** mean age (intervention/control in years): 61/57.9; male gender (intervention/control in %): 23/19.7; married or living with partner (intervention/control in %): 88.5./95.1; education < 9 years (intervention/control in %): 0/1.6; Caucasian (intervention/control in %): 90.2/95.1; employed (intervention/control in %): 37.7/23.3; relationship to patient (intervention/control in %): spouse/partner 78.7/72.1, child 6.6/16.4, sibling 4.9/6.6, parent 6.6/4.9
Interventions	**Name:** early vs. later palliative cancer care: clinical and biobehavioural outcomes (project ENABLE III). All participants received usual oncology care directed by a medical oncologist and consisting of anticancer and symptom control treatments and consultation with oncology and supportive care specialists, including a clinical palliative care team, which was provided whenever requested, regardless of group assignment **Service base:** outpatient palliative care **Intervention condition (n = 104):** ENABLE telehealth concurrent palliative care model within 30 to 60 days of being informed of an advancer cancer diagnosis, cancer recurrence, or progression: initial in-person, standardised outpatient palliative care consultation by a board-certified palliative care clinician and 6 structured weekly telephone coaching sessions by an advanced practice nurse using a manualised curriculum (*Charting Your Course: An Intervention for Patients With Advanced Cancer*); sessions 1 to 3 focussed on problem solving, symptom management, self-care, identification and co-ordination of local resources, communication, decision making, and advance care planning; sessions 4 to 6 comprised Outlook, a life-review approach that encourages participants to frame advanced illness challenges as personal growth opportunities; after the 6 *Charting Your Course* sessions, monthly follow-up calls reinforced prior content and identified new challenges or care co-ordination issues; study principal investigator reviewed all palliative care consultation notes and digitally recorded nurse coach sessions for protocol adherence; principal investigator also met with nurse coaches weekly to review and provide feedback on difficult cases **Control condition (n = 103):** ENABLE telehealth concurrent palliative care model 3 months after being informed of an advancer cancer diagnosis, cancer recurrence, or progression
Outcomes	**Primary endpoints:** patient-reported quality of life (FACIT-Pal) and Trial Outcome Index (TOI), symptom impact (QUAL-E), mood (CES-D), 1-year and overall survival, resource use (patient-reported hospital and intensive care unit days and emergency department visits, decedents' data for the period between last patient-reported assessment and death, chemotherapy use in last 14 days and location of death via medical record review) **Secondary endpoints:** caregiver burden, location of death **Assessment points:** baseline/T0: before randomisation; T1: 3 months from enrolment; T2: 6 months from enrolment; T3: 12 months from enrolment; in terminal decline joint modelling: T1: 12 months before death; T2: 6 months before death; T3: 3 months before death
Notes	**Funding source:** grant no. R01NR011871-01 from the National Institute for Nursing Research; Cancer and Leukemia Group B Foundation Clinical Scholar Award; Foundation for Informed Medical Decision-Making; by grant nos. P30CA023108, UL1 TR001086, and R03NR014915; NIH/NINR Small Research Grant 1R03NR014915-01 (Zhigang Li); Norris Cotton Cancer Center pilot funding; Dartmouth-Hitchcock Section of Palliative Medicine; National Palliative Care Research Center

Bakitas 2015 *(Continued)*

Junior Career Development Award (M.A.B.); grant no. 5R25CA047888 from the University of Alabama at Birmingham Cancer Prevention and Control Training Program (J.N.D.-O.); Mentored Research Scholar grant no. MRSG 12-113-01-CPPB in Applied and Clinical Research from the American Cancer Society (K.D.L.)

Declarations of interest among primary researchers: Mark T. Hegel reported research funding from Johnson & Johnson. Remaining study authors reported no relationships to disclose

Power considerations: At planned study completion date (15 March 2013), final enrolment was 207 because of slower than anticipated accrual. On the basis of final sample size, 3-month detectable differences were 7.7 points for FACIT-Pal and 3.2 points for CES-D and thus was larger than projected in the initial power calculation (target sample size of 360, 80% power to detect a 6-point difference in FACIT-Pal and 2.5-point difference in CES-D based on a *t* test comparing 3-month group differences at a 2-sided alpha of .05). Reduced sample size and power might have impeded detection of differences (type II error) in patient-reported outcomes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Random assignment was on a one-to-one basis using computer-generated randomly permuted treatment assignments with randomly assigned block sizes of two and four stratified by disease (six categories) and enrolment site (four clinics)" Judgement: probably done, as investigators consistently describe the use of random sequences
Allocation concealment (selection bias)	Unclear risk	Original publication does not explicitly address allocation concealment Judgement: unclear risk of bias
Blinding of participants (performance bias)	High risk	Preregistration on clinicaltrials.gov (NCT01245621) says it was an open-label trial that blinded only outcome assessors Judgement: not done
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote from main publication: "Data collectors were blinded to participant group" Judgement: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement: N = 59 completers in intervention group vs N = 54 completers in control group (Fisher's exact test with 2-tailed P = 0.58)
Selective reporting (reporting bias)	Low risk	Judgement: Inventory of Complicated Grief-Short Form (ICG-SF) and Quality of Death and Dying (QODD) as outcomes from clinicaltrials.gov registration not reported in publications so far. Publication does not differentiate between primary and secondary outcomes. However, all key outcomes have been reported. We made a close-call decision favouring low risk at this point against unclear risk of bias
Other bias	Low risk	None detected

Maltoni 2016

Methods	Parallel group cluster-randomised controlled trial (cRCT)

Maltoni 2016 *(Continued)*

Participants	**Country and regions:** Italy, 21 centres **Recruitment:** 29 months, patients with advanced and/or metastatic pancreatic cancer **Inclusion criteria:** diagnosis of inoperable locally advanced and/or metastatic pancreatic; cancer for a maximum of 8 weeks before enrolment; age ≥ 18 years; Eastern Cooperative Oncology Group (ECOG) performance status 0-2; life expectancy > 2 months; candidate for antitumour treatment (chemotherapy or target therapy); newly referred patients **Exclusion criteria:** patients who were already receiving PC; patients who had received prior chemotherapy for metastatic or advanced disease; patients who had participated in a clinical trial **Number of participants enrolled:** N = 186 (89 intervention and 97 control) **Participant characteristics:** N = 186; median age (intervention/control in years): 66/67; male gender (intervention/control in %): 61.5/52.8; married or living with partner (intervention/control in %): 76.9/78.6; ECOG performance status 0, 1, 2 (intervention/control in %): 56.7, 37.1, 6.2/56.2, 39.3, 4.5; differences between intervention and control not statistically significant with respect to age, martial status, and performance status **Diseases (intervention/control in %):** metastatic pancreatic cancer 100/100 **Deaths at end of study (intervention/control in N (%)):** 19 (19.6)/16 (17.8); differences between intervention and control not statistically significant **Withdrawals/other drop-outs (intervention/control in N):** 33/24; differences between intervention and control not statistically significant
Interventions	**Name:** standard cancer care plus on-demand early palliative care or standard cancer care plus systematic early palliative care (interventional arm) **Service base:** 21 Italian centres **Intervention condition (n = 89):** "Patients assigned to the interventional arm had an appointment scheduled with a PC specialist who had a predefined checklist of issues to be addressed during the consultation. The use of the checklist by the individual researcher was not monitored from the outside, but reported by the researcher himself. The checklist of topics to be discussed during the visit of PC is the same used by Temel [4] and is reported in the original protocol. Patients met a member of the PC team within 2 weeks of enrolment and were seen thereafter every 2 to 4 weeks until death. In both arms, availability between appointments not scheduled in the protocol, but according to the clinical and organisational solutions, was present in every centre. Moreover, every researcher could have adjunctive routine tools of assessment, not considered in the present study. Palliative care appointments and interventions were oriented by general PC guidelines [12]. The full-time palliative care specialist who regularly saw interventional arm patients could prescribe drugs and request other interventions pertaining to physical, psychological, and spiritual needs. However, recommendations made by the PC expert on decision making processes had to be shared by the oncologist" **Control condition (n = 97):** "Patients assigned to the standard arm were not scheduled to meet the PC team unless they, their families, or the attending oncologist requested an appointment. After the evaluation period (T1 = 12 +/-3 weeks from T0), patients were followed by the PC team as needed"
Outcomes	**Primary endpoints:** health-related quality of life (Trial Outcome Index, TOI, as sum of scores on the disease-specific subscale and on physical and functional well-being subscales of the Functional Assessment of Cancer Therapy-Hepatobiliary, FACT-Hep) **Secondary endpoints:** mood (Hospital Anxiety and Depression Scale, HADS), family satisfaction with end-of-life care (FAMCARE), end-of-life care aggressiveness (chemotherapy in the last 30 days of life, median duration of hospice admission, death at home or in hospice) **Assessment points:** baseline/T0: before randomisation; T1: 12 +-/+ 3 weeks from enrolment
Notes	**Funding source:** grant no. RF-2011-02350971 from the Italian Ministry of Health

Maltoni 2016 *(Continued)*

Declarations of interest among primary researchers: Study authors declared no conflicts of interest

Power considerations: At study completion, final enrolment was 186 and was somewhat lower than projected in the initial power calculation (target sample size of 240, 80% power on a *t* test comparing treatment groups at a 2-sided alpha of .05, effect size 0.50). Reduced sample size and power might have increased probability of type II error

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible patients were randomised for a maximum of 8 weeks after diagnosis and before anticancer treatment to one of the two groups on a 1:1 allocation rate. Separate randomisation lists using a permuted block balanced procedure were generated for each participating centre" Judgement: probably done
Allocation concealment (selection bias)	Low risk	Quote (reply received from principal investigator): "The random assignment was done by a telephone call to the Biostatistics and Clinical Trials Unit of the coordinating center in Meldola using computer-generated randomization lists of permutated blocks of varying sizes stratified for participating center. The sequences were concealed from the physicians" Judgement: probably done
Blinding of participants (performance bias)	High risk	Quote: "No masking was involved in this open-label trial" Judgement: not done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Original publication does not explicitly address blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement: N = 64 completers in intervention group vs N = 65 completers in control group (Fisher's exact test with 2-tailed P value at 0.34)
Selective reporting (reporting bias)	Low risk	Judgement: all outcomes from clinicaltrials.gov registration listed and reported in publications
Other bias	Low risk	None detected

McCorkle 2015

Methods	Parallel-group cluster-randomised controlled trial (cRCT)
Participants	**Country and regions:** USA, Smilow Cancer Hospital at Yale/New Haven, Connecticut **Recruitment:** 29 months, gynaecological, lung, head and neck, and gastrointestinal clinics, patients identified at weekly tumour boards and approached by their oncologist **Inclusion criteria:** aged 21 years or older; late-stage cancer diagnosis within 100 days; post biopsy or surgery with additional treatment recommended; at least 1 self-reported chronic condition **Exclusion criteria:** not reported **Number of participants enrolled:** N = 146 (66 intervention and 80 control), gynaecological and lung clinics allocated to intervention group, head and neck and gastrointestinal clinics allocated to control group

McCorkle 2015 *(Continued)*

	Participant characteristics: N = 146; age < 65 years (intervention/control in %): 51.5/71.3; age ≥ 65 years (intervention/control in %): 48.5/28.7; male gender (intervention/control in %): 28.8/56.3; married or living with partner (intervention/control in %): 60.6/52.5; education < 9 years (intervention/control in %): 27.3/30.3; employed (intervention/control in %): 30.3/37.5; number of comorbidities between 3 and 12 (intervention/control in %): 63.6/36.2; differences between intervention and control statistically significant with respect to age, gender, and comorbidity **Diseases (intervention/control in %):** lung cancer 25.3/--; gastrointestinal tract --/36.3; gynaecological tumour 19.9/--; head and neck tumour 0/18.5 **Deaths at end of study (intervention/control in N (%)):** 7 (10.6)/3 (3.8); differences between intervention and control not statistically significant **Withdrawals/other drop-outs (intervention/control in N (%)):** 23 (34.8)/21 (26.2); differences between intervention and control not statistically significant
Interventions	**Name:** advanced practice nurse co-ordinated multi-disciplinary intervention vs standard cancer care **Service base:** 4 disease-specific outpatient clinics **Intervention condition (n = 66):** 10-week standardised intervention delivered by different members of each team included monitoring participants' status, providing symptom management, executing complex care procedures, teaching participants and family caregivers, clarifying the illness experience, co-ordinating care, responding to the family, enhancing quality of life, and collaborating with other providers; clinic advanced practice nurses initially contacted participants within 24 hours, and weekly phone and scheduled in-person contacts (5 clinic visits and 5 telephone calls); members of each disease-specific multi-disciplinary team worked together as a palliative care unit, each member taking on different functions to ensure all components of the intervention were addressed; clinic advanced practice nurse oversaw co-ordination and implementation **Control condition (n = 80):** enhanced usual care, i.e. usual multi-disciplinary care plus a copy of the symptom management toolkit with instructions on its use
Outcomes	**Primary endpoints:** symptom distress (Symptom Distress Scale, SDS), health distress (4-item scale developed by the Stanford Patient Education Research Center), depression (Patient Health Questionnaire, PHQ-9), emotional distress (Emotional Distress Thermometer, EDT), functional status (Enforced Social Dependency Scale, ESDS), self-rated health (first item of the SF-12) **Secondary endpoints:** anxiety (7-item Hospital Anxiety and Depression Scale, HADS-Anxiety), self-efficacy (Self-Efficacy for Managing Chronic Disease Scale, SEMCD), uncertainty (Mishel Uncertainty in Illness Scale - Community Form, MUIS-C), quality of life (Functional Assessment of Cancer Therapy - General, FACT-G) **Assessment points:** baseline/T0: after randomisation; T1: 1 month from enrolment; T2: 3 months from enrolment
Notes	**Funding source:** NIH/NINR grant R01NR011872 **Declarations of interest among primary researchers:** Apart from funding, no further study author disclosure statements were made **Power considerations:** No a priori sample size calculation was provided. Small sample size and power might have increased probability of type II error

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from main publication: "Randomization was done using the *ranuni* function in conjunction with the rank procedure in statistical software SAS

McCorkle 2015 *(Continued)*

		(SAS version 9.2 for Windows; SAS Institute Inc., Cary, NC)" Judgement: probably done
Allocation concealment (selection bias)	Unclear risk	Original publication does not explicitly address allocation concealment. Judgement: unclear risk of bias
Blinding of participants (performance bias)	High risk	Preregistration on clinicaltrials.gov (NCT01272024) says it was an open-label trial. Judgement: unclear risk of bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Original publication does not explicitly address blinding of outcome assessment. Judgement: unclear risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement: N = 36 completers in intervention group vs N = 56 completers in control group (Fisher's exact test with 2-tailed P = 0.06). Non-significant trend for higher attrition in the intervention group. We made a close-call decision favouring low risk against high risk of bias
Selective reporting (reporting bias)	High risk	Uncertainty (MUIS-C) as single primary outcome in clinicaltrials.gov registration, reported as secondary outcome in publication. Anxiety (HADS-Anxiety) as single secondary outcome in clinicaltrials.gov registration. Judgement: high risk for reporting bias
Other bias	Low risk	Statistically significant differences between arms with respect to age, gender, and comorbidity at baseline. Judgement: Given the baseline imbalance, recruitment bias may potentially be present. We made a close-call decision favouring low risk for other bias, as high risk for selection bias was already detected

Tattersall 2014

Methods	Parallel-group randomised controlled trial (RCT)
Participants	**Country and regions:** Australia, Department of Medical Oncology, Royal Prince Alfred Hospital (RPAH) Camperdown, New South Wales **Recruitment:** 22 months, no additional details reported **Inclusion criteria:** newly detected incurable metastatic cancer (just diagnosed or relapsed with metastatic disease after previous adjuvant chemotherapy); life expectancy < 12 months (oncologist estimate of patient's likely survival time) **Exclusion criteria:** previous contact with palliative care **Number of participants enrolled:** N = 120 (60 intervention and 60 control) randomised **Participant characteristics:** N = 107; mean age (intervention/control in years): 63/64; male gender (intervention/control in %): 53/43; married or living with partner (intervention/control in %): 67/68; education ≤ 10 years (intervention/control in %): 38/53; oncologist estimate of participant's likely survival time (intervention/control in %): 4-12 weeks 2/0, 3-6 months 15/10, 6-12 months 55/50, > 12 months 18/33, not stated 10/7; intervention group with significantly more recent initial diagnosis and significantly more participants with likely survival time > 12 months **Diseases (intervention/control in %):** lung cancer 20/18; gastrointestinal tract 33/40; breast 8/20; other gynaecological tumour 18/13; prostate 0/3; other tumour 20/5; differences between intervention and control not statistically significant **Deaths at end of study (intervention/control in N (%)):** 39 (65)/31 (51.7); differences between intervention and control not statistically significant

Tattersall 2014 *(Continued)*

	Withdrawals/other drop-outs (intervention/control in N (%)): 36 (60.0)/37 (61.7); differences between intervention and control not statistically significant
Interventions	**Name:** early contact with a palliative care nurse consultant with ongoing oncologist care vs oncologist care alone **Service base:** outpatient palliative care **Intervention condition (n = 60):** meeting with a palliative care nurse consultant member of the hospital palliative care team, who outlined available palliative care services including advice about symptom control, offered to arrange review by a palliative care physician, and provided contact details for the palliative care service; palliative care nurse offered to telephone the participant monthly to check on his or her well-being, or, if the participant preferred, provided contact details for use by participant; standard oncological care given consistent with the oncologist's recommendation **Control condition (n = 60):** referral to the palliative care service when recommended by the oncologist
Outcomes	**Primary endpoints:** symptom severity (Rotterdam Symptom Checklist, RSC), quality of life (McGill Quality of Life Questionnaire, MQOL), degree of perceived support (Supportive Care Needs – Short Form questionnaire, SCNS-SF34) **Secondary endpoints:** hospital medical records including end-of-life experiences, number of lines of chemotherapy, place of death **Assessment points:** baseline/T0: after randomisation; T1: 1 month from enrolment; T2: 3 months from enrolment; T3: 6 months from enrolment; T4: 9 months from enrolment; T5: 12 months from enrolment
Notes	**Funding source:** National Health & Medical Research Council strategic palliative care research grant no. 219141 **Declarations of interest among primary researchers:** Apart from funding, no additional study author disclosure statements were made **Power considerations:** At study completion, final enrolment was 120 owing to slower accrual than was projected in the initial power calculation (target sample size of 150, 80% power on a *t* test comparing treatment groups at a 2-sided alpha of .05, effect size 0.50). Reduced sample size and power might have increased probability of type II error

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from main publication: "For allocation of the participants, a computer-generated list of random numbers was used, and allocation was concealed using sequentially numbered, opaque sealed envelopes. No stratification was made for oncologist or cancer diagnosis" Judgement: probably done
Allocation concealment (selection bias)	Low risk	Quote from main publication: "allocation was concealed using sequentially numbered, opaque sealed envelopes" Judgement: probably done
Blinding of participants (performance bias)	High risk	Registration in the Australian New Zealand Clinical Trial Registry (ACTRN12611001137987) says it was an open-label trial. Judgement: not done
Blinding of outcome assessment (detection bias)	Unclear risk	Original publication does not explicitly address blinding of outcome assessment

Tattersall 2014 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	High risk	Judgement: N = 21 completers in intervention group vs N = 29 completers in control group (Fisher's exact test with 1-tailed P = 0.19). However, we assumed high risk of bias due to high loss of follow-up across both groups
Selective reporting (reporting bias)	Unclear risk	Judgement: Outcomes from Australian New Zealand Clinical Trials Registry (ANZCTR) listed and reported in publications. However, trial registration was conducted after recruitment of participants. We made a close-call decision favouring unclear risk against high risk of bias
Other bias	Unclear risk	Quote: "Most baseline characteristics were adequately balanced across the two study groups (Table 1), however there were differences between the groups in the time since initial cancer diagnosis (mean of 29 versus 34 months in the early referral and standard care groups respectively), and the oncologists' estimate of likely survival (i.e. 11 versus 20 patients with estimates of > 12 months likely survival in the early referral and standard care groups respectively). Therefore, these variables were controlled for in subsequent analyses. There were no remarkable baseline differences on the patient reported outcome measures between the groups" Judgement: Given the baseline imbalance, recruitment bias may potentially be present. However, accounting for imbalance in statistical analysis did not change results. Thus, we made a close-call decision favouring unclear risk against high risk of bias

Temel 2010

Methods	Parallel-group randomised controlled trial (RCT)
Participants	**Country and regions:** USA, Massachusetts General Hospital, Boston, Massachusetts **Recruitment:** 38 months; patients who presented to the outpatient thoracic oncology clinic were invited by their medical oncologists; all medical oncologists in the clinic agreed to approach, recruit, and obtain consent from their patients; physicians were encouraged, but were not required, to offer participation to all eligible patients; no additional screening or recruitment measures were used **Inclusion criteria:** pathologically confirmed metastatic non-small cell lung cancer; diagnosis within previous 8 weeks; Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; able to read and respond to questions in English **Exclusion criteria:** patients already receiving care from the palliative care service **Number of participants enrolled:** N = 151 (77 intervention and 74 control) **Participant characteristics:** N = 151; mean age (intervention/control in years): 64.9/65.0; male gender (intervention/control in %): 51/45; married or living with partner (intervention/control in %): 61/62; Caucasian (intervention/control in %): 95/100; differences between intervention and control not statistically significant **Diseases (intervention/control in %):** non-small cell lung cancer 100/100; presence of brain metastases 26/31; receipt of initial chemotherapy as part of a clinical trial 27/21; never smoked or smoked ≤ 10 packs/y 22/24; illness perception of curable cancer 32/31; differences between intervention and control not statistically significant **Deaths at end of study (intervention/control in N (%)):** 10 (13.0)/17 (23.0); differences not statistically significant (P = 0.14) **Withdrawals/other drop-outs (intervention/control in N(%)):** 7 (9.1)/10 (13.5); differences not statistically significant

Temel 2010 *(Continued)*

Interventions	**Name:** early palliative care integrated with standard oncological care as compared with standard oncological care alone. All participants continued to receive routine oncological care throughout the study period **Service base:** outpatient palliative care **Intervention condition (n = 77):** "Patients who were assigned to early palliative care met with a member of the palliative care team, which consisted of board-certified palliative care physicians and advanced-practice nurses, within 3 weeks after enrolment and at least monthly thereafter in the outpatient setting until death. Additional visits with the palliative care service were scheduled at the discretion of the patient, oncologist, or palliative care provider. General guidelines for the palliative care visits in the ambulatory setting were adapted from the National Consensus Project for Quality Palliative Care and were included in the study protocol. Using a template in the electronic medical record, palliative care clinicians documented the care they provided according to these guidelines. Specific attention was paid to assessing physical and psychosocial symptoms, establishing goals of care, assisting with decision making regarding treatment, and coordinating care on the basis of the individual needs of the patient" **Control condition (n = 74):** "Patients who were randomly assigned to standard care were not scheduled to meet with the palliative care service unless a meeting was requested by the patient, the family, or the oncologist; those who were referred to the service did not cross over to the palliative care group or follow the specified palliative care protocol"
Outcomes	**Primary endpoints:** quality of life (Trial Outcome Index, TOI, as sum of scores on the Lung Cancer Subscale and on physical and functional well-being subscales of the Functional Assessment of Cancer Therapy-Lung, FACT-L) **Secondary endpoints:** mood (Hospital Anxiety and Depression Scale, HADS; Patient Health Questionnaire 9, PHQ-9), healthcare use and end-of-life care (anticancer therapy, medication prescriptions, referral to hospice, hospital admissions, emergency department visits, date and location of death), aggressive care, participants' resuscitation preferences **Assessment points:** baseline/T0: before randomisation; T1: 3 months from enrolment
Notes	**Funding source:** American Society of Clinical Oncology Career Development Award and philanthropic gifts **Declarations of interest among primary researchers:** Apart from funding, no additional study author disclosure statements were made **Power considerations:** Primary outcome was change in score on the TOI from baseline to 12 weeks. Study authors estimated that with 120 participants, the study would have 80% power to detect a significant between-group difference in the change in TOI score from baseline to 12 weeks, with a medium effect size of 0.5, SD.24. Protocol was amended in August 2008 to allow for enrolment of 30 additional participants to compensate for loss of any participants to follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	According to a reply received from the principal investigator, computer-generated random sequence generation with no stratification was applied. Judgement: probably done
Allocation concealment (selection bias)	High risk	According to a reply received from the principal investigator, no allocation concealment. Judgment: not done

Temel 2010 *(Continued)*

Blinding of participants (performance bias)	High risk	Preregistration on clinicaltrials.gov (NCT01038271) says it was an open-label trial. Judgement: not done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Original publication does not explicitly address blinding of outcome assessment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement: N = 60 completers in intervention group vs N = 47 completers in control group (Fisher's exact test with 2-tailed P value at 0.07). Trend toward higher attrition in the control group
Selective reporting (reporting bias)	Low risk	Judgement: All outcomes from clinicaltrials.gov registration listed and reported in publications
Other bias	Low risk	None detected

Zimmermann 2014

Methods	**Study design:** parallel-group cluster-randomised controlled trial (cRCT)
Participants	**Country and regions:** Canada, Princess Margaret Cancer Centre, University Health Network Toronto, Ontario **Recruitment:** 51 months, daily screening of participating oncology clinics by research personnel **Inclusion criteria:** aged 18 years or older; stage IV cancer (refractory to hormonal therapy as additional criterion for breast or prostate cancer, patients with stage III cancer and poor clinical prognosis were included at the discretion of the oncologist); estimated survival of 6-24 months (assessed by main oncologist); ECOG performance status of 0, 1, or 2; completed baseline measures **Exclusion criteria:** insufficient English literacy; inability to pass the cognitive screening test (Short Orientation-Memory-Concentration Test score < 20 or > 10 errors) **Number of participants enrolled:** N = 461 (228 intervention and 233 control), 12 clinics allocated to intervention and control groups, respectively **Participant characteristics:** N = 461; mean age (intervention/control in years): 61.2/60.2; male gender (intervention/control in %): 40.4/46.4; married or living with partner (intervention/control in %): 68.4/71.7; education < 9 years (intervention/control in %): 8.0/10.3; employed (intervention/control in %): 19.7/25.3; differences between intervention and control not statistically significant **Diseases (intervention/control in %):** lung cancer 24.1/19.7; gastrointestinal tract 32.5/27.9; genitourinary 11.8/21.9; breast 18.0/13.3; other gynaecological tumour 13.6/17.2; control group with significantly larger number of participants with genitourinary cancers .02 **Deaths at end of study (intervention/control in N (%)):** 26 (11.4)/44 (18.9); differences statistically significant at P = 0.02 **Withdrawals/other drop-outs (intervention/control in N (%)):** 52 (22.8)/53 (22.7); differences between intervention and control not statistically significant
Interventions	**Name:** early intervention in patients with advanced cancer by a palliative care team vs standard cancer care **Service base:** outpatient clinics, hospital service, home care

Zimmermann 2014 *(Continued)*

	Intervention condition (n = 228): multi-disciplinary approach to care addressing physical, psychological, social, and spiritual needs *Outpatient clinics:* palliative care physician and nurse; routine visits once monthly and more often if necessary; routine structured symptom assessment in clinic during every visit by palliative care nurse and physician; routine psychosocial assessment in clinic and discussion of goals of care, of participant and family support needs, and of participant and family coping and psychological distress; discussion of advance care planning according to participant and family readiness; routine telephone follow-up by palliative care nurse after each visit; more often as needed by palliative care nurse and physician; 24-hour on-call service explained during first visit, provided by specialised palliative care physicians *Hospital service:* direct access to palliative care unit for symptom management; primary care by trained palliative care nurses and physicians; formal 10-day training for staff at opening of palliative care unit and continued education by palliative care unit advanced practice nurse; follow-up by palliative care team when admitted to non-palliative care unit service at University Health Network. *Home care:* community care access centre services explained and offered during first visit, reassessed at each visit; routine communication with family physician and community care access centre; home palliative care physician was explained during first visit and was offered with ECOG performance status ≥ 3 or when participant requested **Control condition (n = 233):** approach to care mainly via addressing physical needs *Outpatient clinics:* oncologist and oncology nurses; visits ad hoc and mainly based on chemotherapy or radiation schedule; no structured symptom assessment; no routine psychological assessment; follow-up as needed and conducted by oncology nurse, rare access to oncologist; access to 24-hour on-call service (oncology resident or clinical associate). *Hospital service:* no access to palliative care unit; admission to oncology ward or medical ward (via emergency department for urgent care); primary care by oncology nurses and clinical associates; no formal palliative care training; no follow-up by palliative care team. *Home care:* community care access centre services ad hoc; generally no home care referral until referral to palliative care team; rarely an ad hoc communication with family physician and community care access centre; no home palliative care physician
Outcomes	**Primary endpoints:** participant-reported quality of life (Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being, FACIT-Sp and Quality of Life at the End of Life, QUAL-E) **Secondary endpoints:** symptom impact (Edmonton Symptom Assessment System, ESAS), participant interaction with nurses and doctors (Cancer Rehabilitation Evaluation System Medical Interaction Subscale, CARES-MIS), satisfaction with care (family satisfaction with advanced cancer care, FAMCARE-P16) **Assessment points:** baseline/T0: after randomisation; T1: 1 month from enrolment; T2: 2 months from enrolment; T3: 3 months from enrolment; T4: 4 months from enrolment
Notes	**Funding source:** Canadian Cancer Society, Ontario Ministry of Health and Long Term Care **Declarations of interest among primary researchers:** Study authors declared no competing interests **Caregiver assessment:** data from caregivers collected for an exploratory substudy, publication pending **Power considerations:** Initial sample size estimation showed that 380 participants (190 per group) would provide 80% power at the 2-sided 5% level of significance to detect a between-group difference in FACIT-Sp of 0.45 SD (medium effect size) by the primary endpoint of 3 months. Sample size was recalculated in 2008, on the basis of observed SD (from aggregated baseline data of 245 participants), intracluster correlation coefficient, attrition, and adherence. Revised sample size was 450 participants (225 per group)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from main publication: "Randomisation was done by the statistical team at Western University (London, ON, Canada) using a computer-generated sequence, was in a 1:1 ratio, and was stratified by clinic size and tumour site [...]"

Zimmermann 2014 *(Continued)*

		Judgement: probably done
Allocation concealment (selection bias)	High risk	Quote from main publication: "There was also selection bias, which is common in cluster-randomised studies because of randomisation of clusters before consent of individuals. A larger number of patients declined participation in the intervention group because of lack of symptoms" Judgement: probably not done
Blinding of participants (performance bias)	Low risk	Quote from main publication: "Although complete masking of interventions was not possible, patients provided written informed consent to participate in their own study group, without being informed of the existence of another group. This form of masking is common in cluster randomised trials, and avoids potential bias from patients in the control group requesting the intervention or otherwise altering their behaviour" Judgement: probably done
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote from main publication: "Oncologists and investigators were aware of assignment" Judgement: probably not done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Judgement: N = 131 completers in intervention group vs N = 155 completers in control group (Fisher's exact test with 2-tailed P value at 0.05). By conventional criteria, higher attrition in the intervention group of borderline significance. We made a close-call decision favouring low risk against high risk of bias
Selective reporting (reporting bias)	Low risk	Judgement: Functional Assessment of Cancer Therapy-General (FACT-G) as primary outcome in clinicaltrials.gov registration, FACIT-Sp (includes FACT-G) reported as primary outcome in publications so far. Secondary outcomes Caregiver Quality of Life Index-Cancer (CQOL-C) and SF-36 not reported in publications so far. However, all key outcomes have been reported
Other bias	Low risk	Tendency for higher outcome measure scores (for FACIT-Sp at P = 0.03; for ESAS at P < 0.001; for FAMCARE-P16 at P < 0.001) in intervention group at baseline. Larger number of participants with genitourinary cancers in the control group at baseline. No loss of clusters reported Judgement: Given the baseline imbalance, recruitment bias may potentially be present. We made a close-call decision favouring low risk for other bias, as high risk for selection bias was already detected

g/dL: grams per decilitre
µg/mL: microgram per millilitre
N = number of participants
packs/y: packs per year
PC: palliative care
SD: standard deviation

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Badr 2015	Psychosocial intervention focussing on dyadic coping. No genuine multi-dimensional palliative care approach

Study	Reason for exclusion
Brumley 2007	No outcome measurement regarding symptom intensity or quality of life
Caruso 2014	Psychotherapy only. No genuine multi-dimensional palliative care approach
Dyar 2012	Discussions of the benefits of hospice and advanced directives, led by a single nurse only. No genuine multi-dimensional palliative care approach
Ferrell 2015	Non-randomisation, instead quasi-experimental trial with sequential enrolment of patients into control and intervention groups
Gade 2008	Study followed a conventional palliative care approach. No genuine early palliative care intent
Grudzen 2016	ED-initiated palliative care consultation. No genuine early palliative care intent
Jensen 2014	Aerobic exercise, resistance or respiratory training only. No genuine multi-dimensional palliative care approach
Jordhoy 2001	Portion of patient sample in the terminal phase. Study followed a conventional palliative care approach. No genuine early palliative care intent
Laing 1975	Randomised prospective trial comparing "no immediate treatment" with single- and multiple-agent chemotherapy. However, study did not follow a proactive palliative care intent as characteristic for early palliative care
Lloyd-Williams 2013	Psychosocial intervention applying narrative interviews. No genuine multi-dimensional palliative care approach
Mok 2012	Portion of patient sample in the terminal phase. Study followed a conventional palliative care approach. No genuine early palliative care intent
NCT02311465	Investigators withdrew the study before enrolment
Pantilat 2010	Study followed a conventional palliative care approach. No genuine early palliative care intent
Rabow 2004	Patient sample had a life expectancy of 1 to 5 years and varying diseases. No genuine early palliative care intent
Rummans 2006	No explicit focus on physical domain/symptom control. No genuine early palliative care intent
Schofield 2013	Portion of patient sample in the terminal phase. Study followed a conventional palliative care approach. No genuine early palliative care intent
Stein 2005	Psychosocial intervention only. No genuine multi-dimensional palliative care approach
Thoonsen 2011	Ongoing implementation study in which general practitioners were randomised. We do not consider this study to be a clinical trial on a patient population
Toseland 1995	Psychosocial intervention only. No genuine multi-dimensional palliative care approach
Young 2013	Telephone follow-up intervention for postoperative patients with colorectal cancer. Most patients with prognosis longer than 24 months. No genuine early palliative care intent

Characteristics of studies awaiting assessment *[ordered by study ID]*

Aljohani 2015

Methods	RCT
Participants	Patients with newly diagnosed NSCLC have a high symptom burden, poor quality of life, and a prognosis less than 1 year
Interventions	Early palliative care integrated with standard oncological care
Outcomes	Primary outcome measures: quality of life at 12 weeks assessed with the ESAS
Notes	Abstract with results published. We found no preregistration entry for this study

Groenvold 2017

Methods	RCT
Participants	Patients in contact with oncology departments who had cancer stage IV according to the 'TNM' (tumour, node, metastases) classification or cancer in the central nervous system grade 3 or 4, were at least 18 years of age, lived in the area of one of the participating specialised palliative care centres, and had not had contact with an SPC during the previous year received a screening questionnaire. If, according to their answers on the questionnaire, patients had a palliative need and 4 additional symptoms (see definition below), they were informed about the study and were invited to participate. Patients were excluded from the study if they could not understand Danish well enough to complete a questionnaire or were considered incapable of complying with the study protocol
Interventions	*Experimental condition:* specialised palliative care *Control condition:* standard care
Outcomes	All randomised participants are assessed at baseline (the screening); after a 3-week follow-up period; and after an 8-week follow-up period. The *primary outcome* is estimated as the difference between intervention and control groups in the change from baseline to the weighted mean of the 3- and 8-week follow-up measured as area under the curve for the EORTC QLQ-C30 scale score that constitutes the primary need. The primary need is defined as the palliative need having the highest intensity at baseline according to the EORTC QLQ-C30. *Secondary outcomes*, estimated in the same way, are remaining symptoms and problems measured by the EORTC QLQ-C30 (14 scales); anxiety and depression measured by the HADS; participants' evaluation of treatment and care provided by the healthcare system and measured by FAMCARE-P16; survival; and economical consequences per week from the start of the study to minimum 3 months after the end of the intervention
Notes	Study completed. Protocol published

Kim 2016

Methods	Non-randomised parallel assignment
Participants	*Inclusion criteria:* • Diagnosis of stage I-IIIA resectable NSCLC - undergoing lobectomy, pneumonectomy, segmentectomy, or wedge resection • Living within a 50-mile radius of the City of Hope • No previous cancer within the past 5 years *Exclusion criteria:*

Kim 2016 *(Continued)*

	• Diagnosis of stage II-III NSCLC that is not resectable based on clinical and individual characteristics (comorbidities, extent of disease, bulky mediastinal lymph nodes (N2), etc.) • Patients with NSCLC receiving radiofrequency ablation
Interventions	*Experimental condition:* group II (palliative care intervention); participants receive an individualized interdisciplinary palliative care intervention combining patient-centred teaching principles and concepts that are learner-entered (builds on strengths, interests, and needs of the learner), knowledge-entered (teacher is proficient in the content being taught), assessment-entered (learners are given an opportunity to test their understanding and receive feedback), and community-entered (opportunities are available for continued learning and support); patients undergo 4 teaching sessions (based on patient-entered teaching principles and concepts) that focus on physical, psychological, social, and spiritual well-being, respectively, once a week in weeks 3-6; patients then receive 4 follow-up phone calls in weeks 9-21 to clarify questions or review concerns from teaching sessions and to co-ordinate follow-up resources as needed *Control condition:* group I (standard care); participants receive standard care; participants complete questionnaires at baseline and at 6, 12, 24, 36, and 52 weeks to evaluate quality of life (QOL), symptoms, psychological distress, and geriatric assessments
Outcomes	*Primary outcome measures:* overall quality of life and psychological distress at 6 months; symptom control at 6 months; geriatric assessment outcomes (OARS (Older Americans' Resources and Services) Instrumental Activities of Daily Living, MOS (Medical Outcomes Study) Activities of Daily Living, MOS Social Activities Limitation Scale, HADS scores, and Karnofsky performance scale); resource use (chart audits)
Notes	Study completed and results published.

Meyers 2011

Methods	Multi-site RCT
Participants	*Inclusion criteria:* • Adults with relapsed, refractory, or recurrent solid tumours or lymphoma • Enrolled onto phase 1 or 2, or phase 3 trials that compared therapy for advanced cancer *Exclusion criteria:* • Patients receiving concomitant chemotherapy and radiation • Patients on adjuvant phase III studies • Patients with hematopoietic malignancies • Patients with primary brain tumours • Patients not fluent in English • Patients < 18 years of age or lacking a willing caregiver
Interventions	*Experimental condition:* "intervention arm dyads received a copy of *The Home Care Guide for Cancer*. Each book chapter addresses a problem known to affect patients with cancer including physical symptoms (pain or nausea), psychological symptoms (anxiety or depression), or issues related to resources or relationships, including communicating with one's health care team or getting support or services from family, friends, and community organizations. Each chapter follows the same problem-solving formula..Each educational session included the trained educator, the patient, and [the] designated caregiver. The first educational session was conducted up to 7 days prior to or on the day the patient started [the] investigational clinical trial. The first session focussed on becoming familiar with the guide and the COPE (Creativity, Optimism, Planning and Expert information) problem-solving model, using COPE to address a patient or caregiver-identified problem. The two additional conjoint instructional sessions were conducted within the first 30 days, reinforcing this learning by focusing on two addi-

Meyers 2011 *(Continued)*

	tional patient or caregiver-identified problems. Dyads could use one of the problems in the book's chapters, or identify another problem and apply the model. In either event, the instructors facilitated this process of using the Guide and the COPE model, being careful not to solve the problem for them. Following each session, the educator documented the problem and recorded process notes" *Control condition:* "usual care"
Outcomes	*Primary outcome measures:* City of Hope (COH) quality of life (QOL) instruments for patients or caregivers and the social problem solving inventory revised
Notes	Study completed. Results published. We contacted study authors for explicit information on palliative care intent. The reply to this study author request is pending

NCT00823732

Methods	Non-randomised parallel assignment
Participants	*Inclusion criteria:* • Confirmed metastatic lung cancer (NSCLC, small cell lung cancer, and mesothelioma) or non-colorectal gastrointestinal cancer (oesophageal, gastric, and hepatobiliary) not being treated with curative intent • Informed of metastatic disease within previous 8 weeks • No prior therapy for metastatic disease • Able to read questions in English or willing to complete questionnaires with the assistance of an interpreter • Relative or friend of participant who will likely accompany the participant to clinic visits *Exclusion criteria:* • Significant psychiatric or other comorbid disease
Interventions	*Experimental condition:* phase 2 intervention GROUP II (palliative care intervention); participants receive an individualised interdisciplinary palliative care intervention comprising learner-centred, knowledge-centred, assessment-centred, and community-centred concepts; participants undergo 4 teaching sessions, focussed on physical, psychological, social, and spiritual well-being, once weekly in weeks 3-6; participants then receive 4 follow-up phone calls in weeks 9, 13, 17, and 21 *Control condition:* no Intervention; phase I usual care GROUP I (usual care); participants receive standard care
Outcomes	*Primary outcome measures:* overall quality of life and psychological distress at 6 months; symptom control at 6 months; geriatric assessment outcomes (OARS (Older Americans' Resources and Services) Instrumental Activities of Daily Living, MOS (Medical Outcomes Study) Activities of Daily Living, MOS Social Activities Limitation Scale, Hospital Anxiety and Depression Scale scores, and Karnofsky performance scale); resource use (chart audits)
Notes	Study completed. Publication in preparation according to study authors

NCT01444157

Methods	RCT
Participants	*Inclusion criteria:*

NCT01444157 *(Continued)*

	At least 1 of the following • Cancer stage III or IV (according to hospital journal) and at least 1 treatment after relapse without satisfying effect on the disease • Patient is aware that further treatment is of palliative or life-prolonging nature And also all of the following inclusion criteria: • Patient has a family member who would like to participate (family member must be involved in patient care at least 2 times a week) • At least 18 years old (patient and family member) • Understand and speak Danish (patient and family member) • Live in the area of the municipalities of Copenhagen or Frederiksberg • Discharge from hospital to own home • Written informed consent (patient and family member) *Exclusion criteria:* • Terminal phase of disease • Contact with specialised palliative care • Incapable of co-operating with study protocol • Participant in another behavioural intervention study
Interventions	*Experimental condition:* palliative home care nursing group; in addition to standard home care nursing, families will receive 6 home visits from a research nurse with at least 1 year specialised palliative care experience; during the first 2-hour visit, a family assessment is obtained that identifies family roles, resources, and coping strategies; the first home visit takes place no later than 1 week after randomisation; visits continue every third week up to 16 weeks, each visit with a duration of 1.5 hours; at every visit, the EORTC-QLQ-C30 patient-administered questionnaire is used to identify the nature, frequency, and intensity of the patient's physical and psychosocial problems *Control condition:* standard home care nursing group; patients continue to receive standard home care nursing; they can contact municipality services for visitation to home care nursing if they feel that additional home care is needed, or if they do not yet receive this service and feel they need home care nursing
Outcomes	*Primary outcome measures:* participant-reported health-related quality of life (EORTC QLQ-C30 in relation to the global health status scale) at baseline, week 9, week 16, and week 24 *Secondary outcome measures:* participant-reported symptoms and problems (EORTC QLQ-C30 in relation to its functional scales and symptom scales/items) at baseline, week 9, week 16, and week 24; participant and family member symptoms of anxiety and depression (Hospital Anxiety and Depression Scale) at baseline, week 9, week 16, and week 24; family members' health-related quality of life (SF-36) at baseline, week 9, week 16, week 24, and 12 months; family satisfaction with healthcare services provided to the participant (FAMCARE) at baseline, week 9, week 16, week 24, and 12 months; acute readmission to hospital at weeks 16 and 24
Notes	Study completed. According to the principal investigator, publications are in preparation

NCT02133274

Methods	RCT
Participants	*Inclusion criteria:* • Age ≥18 years and <75 years • Adequate knowledge about the cancer diagnosis • Starting first-line palliative antineoplastic treatment

NCT02133274 *(Continued)*

- Eastern Cooperative Oncology Group Performance Status ≤ 2
- Life expectancy > 6 months and < 24 months (as per the medical oncologist)
- Must have one of the following diagnoses:
  - metastatic or unresectable recurrent breast cancer
  - stage IIIC or IV recurrent platinum-resistant ovarian cancer
  - metastatic or unresectable recurrent cervix cancer
  - metastatic or unresectable recurrent endometrial cancer
  - metastatic or unresectable recurrent head and neck cancer (after previous radiotherapy)
  - hormone-refractory metastatic or unresectable recurrent prostate cancer
  - metastatic or unresectable recurrent genitourinary cancer
  - metastatic or unresectable recurrent non-small cell lung cancer
  - extensive-stage or recurrent small cell lung cancer
  - metastatic or unresectable recurrent gastrointestinal cancer

Exclusion criteria:

- Currently undergoing any psychological treatment owing to a psychological disorder
- Currently using antidepressants to treat depressive disorders and/or anxiety
- Any cognitive deficit or attention problem that could interfere with ability to complete questionnaires or understand study aims (as per investigator)
- Current or previously established diagnosis of any of the following psychological conditions: substance-related disorders; schizophrenia and other psychotic disorders; mood disorders (depressive disorders, bipolar disorders); anxiety disorders; dissociative disorders; personality disorders; and/or history of a suicide attempt
- Patients with single resected metastasis
- Any comorbid condition, which, in the opinion of the investigator, could interfere with safety, compliance with the study, or interpretation of the results
- Patients unable to go to the hospital for study visits, regardless of the reason

Interventions	*Experimental condition 1:* early palliative care; a first medical consult at the palliative care service will be scheduled after 2 to 3 weeks from study inclusion and every 3 to 4 weeks thereafter *Experimental condition 2:* psychosocial plus early palliative care; 5 weekly sessions of a brief psychosocial intervention based on cognitive-behavioural therapy plus early palliative care; regarding early palliative care, a first medical consult at the palliative care service will be scheduled after 2 to 3 weeks from study inclusion and every 3 to 4 weeks thereafter *Control condition:* no Intervention; standard oncological care
Outcomes	*Primary outcome measures:* change from baseline in depression symptoms (HADS, PHQ-9) at day 90; change from baseline in satisfaction with care on the FAMCARE-patient scale at days 45, 90, 120, and 180; descriptive results about feasibility of the study *Secondary outcome measures:* change from baseline in depressive symptoms on HADS-D and PHQ-9 at days 45, 120, and 180; change from baseline in anxiety symptoms on the HADS-A at days 45, 90, 120, and 180; proportion of participants answering that their cancer is curable as measured with an adapted instrument to evaluate cancer understanding at 90, 120, and 180 days; change from baseline in cancer symptoms on the ESAS-br at days 45, 90, 120, and 180; change from baseline in quality of life on the EORTC QLQ-C15-Pal at days 45, 90, 120, and 180
Notes	Last updated on ClinicalTrials.gov on 12 February 2017: "This study has been terminated. Planned interim analysis did not show the expected benefit of intervention A over B (effect size <0.2)."

NCT02207322

Methods	RCT

NCT02207322 *(Continued)*

Participants	*Inclusion criteria:* • Patient eligibility criteria: adult patients (≥ 18 years) with haematological malignancy admitted to MGH for HSCT; ability to speak English or able to complete questionnaires with minimal assistance required from an interpreter or family member • Caregiver eligibility criteria: adult caregivers (≥ 18 years) of patients undergoing HSCT at MGH who agreed to participate in study; a relative or a friend, identified by the patient, who lives with the patient or has in-person contact with him or her at least twice per week; ability to read questions in English or willing to complete questionnaires with the assistance of an interpreter *Exclusion criteria:* • Patients with prior history of HSCT • Patients undergoing HSCT for a benign haematological condition (myelodysplastic syndrome is not considered a benign haematological condition and patients with myelodysplastic syndrome are eligible for the study) • Significant uncontrolled psychiatric disorder (psychotic disorder, bipolar disorder, major depression) or other comorbid disease (dementia, cognitive impairment), which the treating clinician believes prohibits informed consent or participation in the study • Patients enrolled in other supportive care intervention trials
Interventions	*Experimental condition:* • Standard transplant oncology care with early palliative care • Participant enrolment and caregiver enrolment (within 72 hours of participant enrolment) • Longitudinal data collection (participant and family caregivers) *Control condition*: Standard transplant oncology care with participant enrolment and caregiver enrolment (within 72 hours of participant enrolment) and longitudinal data collection (participants and family caregivers)
Outcomes	*Primary outcome measures:* change in FACT-BMT score at 2 weeks, comparison of changes in quality of life (FACT-BMT) scores from baseline to week 2 (day+5 for autologous, day+8 for myeloablative or reduced intensity allogeneic HSCT) between study arms by the 2-sample *t*-test
Notes	Study completed. Abstract with results published. Last updated on ClinicalTrials.gov on 28 January 2017: "This study is ongoing, but not recruiting participants."

Temel 2017

Methods	RCT
Participants	*Inclusion criteria:* • Confirmed metastatic lung cancer (NSCLC, small cell lung cancer, and mesothelioma) or non-colorectal gastrointestinal cancer (oesophageal, gastric, and hepatobiliary) not being treated with curative intent • Informed of metastatic disease within previous 8 weeks • No prior therapy for metastatic disease • Able to read questions in English or willing to complete questionnaires with the assistance of an interpreter • Relative or friend of patient who will likely accompany the patient to clinic visits *Exclusion criteria:*

Temel 2017 *(Continued)*

	• Significant psychiatric or other comorbid disease
Interventions	*Experimental condition:* early palliative care; participants receive standard care with early palliative care *Control condition:* no intervention; participants receive standard of care
Outcomes	*Primary outcome measures:* quality of life (FACT) at baseline and at 12 weeks *Secondary outcome measures:* quality of life (FACT) with change from baseline over 24 weeks; mood (HADS) at baseline, and at 12 and 24 weeks; prognostic understanding at baseline, and at 12 and 24 weeks; family caregiver quality of life (SF-36) at baseline, and at 12 and 24 weeks; family caregiver mood (HADS) at baseline, and at 12 and 24 weeks; family caregiver prognostic understanding at 12 and 24 weeks; resource utilisation at the end of life; chemotherapy utilisation at the end of life; hospice utilisation; healthcare costs; code status documentation; coping (Brief Cope) at baseline, and at 12 and 24 weeks; lung cancer-specific quality of life (FACT-Lung) at 12 and 24 weeks, GI cancer-specific quality of life (FACT-hepatobiliary and FACT-espophageal) at 12 and 24 weeks *Other outcome measures:* additional resource utilisation, hospital admissions, emergency room admissions, intensive care unit admissions, resuscitation attempts, survival
Notes	Study completed and results published.

Van Arsdale 2016

Methods	RCT
Participants	All patients defined as having high risk of gynaecological malignancies (< 30% 5-year predicted survival)
Interventions	Referred to palliative care consultation within 8 weeks of tumour board registration for primary occurrence or recurrence
Outcomes	*Primary outcome measure:* increase in palliative consultation from historical 50% as reported at the tertiary care institution
Notes	Study completed. Abstracts with results published,

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EORTC QLQ-C15-Pal: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Palliative Cancer Care Patients
ESAS: Edmonton Symptom Assessment System
FACT: Functional Assessment of Cancer Therapy
FACT-BMT: Functional Assessment of Cancer Therapy - Bone Marrow Transplant
FAMCARE: Family Satisfaction with Advanced Cancer Care Questionnaire
HADS: Hospital Anxiety and Depression Scale
HSCT: Haematopoietic stem cell transplantation
MGH: Massachusetts General Hospital (MGH)
NSCLC: non-small cell lung cancer
PHQ-9: Patient Health Questionnaire
RCT: randomised controlled trial
SF-36: Short Form (36) Health Survey

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12610000724077

Trial name or title	**Improving communication and quality of life (QOL) at the end of life: a randomised controlled trial of a multifocal communication intervention for patients with advanced incurable cancer, carers and doctors**
Methods	Parallel-group RCT
Participants	Patients are eligible if they have been given the diagnosis of any type of cancer, and their medical oncologist believes they have a life expectancy of between 2 and 12 months. Caregivers are eligible if they are identified as the primary, informal providers of care to a patient participating in the study. Patients and caregivers must read and speak English well enough to be interviewed and to complete questionnaires without the aid of an interpreter, must be over the age of 18 years, and must be capable of giving informed consent. Patients and caregivers will be excluded if they do not speak English or have significant psychological morbidity or cognitive impairment
Interventions	Guided by the self-determination theory of health-behaviour change, the communication support programme pairs a purpose-designed Question Prompt List (an evidence-based list of questions participants/caregivers can ask clinicians) with nurse-led exploration of Question Prompt List content, communication challenges, participant values and concerns, and the value of early discussion of end-of-life issues. Oncologists are also cued to endorse participant and caregiver questions and use of the QPL. Behavioural and self-report data will be collected from participants/caregivers approximately quarterly for up to 2.5 years, or until participant death, after which participant medical records will be examined. Analyses will examine the impact of the intervention on participants' and caregivers' participation in medical consultations, their self-efficacy in medical encounters, quality-of-life, end-of-life care receipt, and quality-of-death indicators
Outcomes	*Patients:* demographic details, communication self-efficacy (Perceived Efficacy in Patient Physician Interactions Scale), quality of life (FACT-G, and the McGill Quality of Life Scale), preferences for information and involvement in decisions about care as well as achievement of preferences for information and involvement in decisions (Degner Control Preference Scale, Cassileth Information Styles Questionnaire), hopes for treatment, preferences for future interventions, acceptance of disease (Peace, Equanimity and Acceptance in the Cancer Experience Scale), understanding of prognosis, doctor's communication skills and manner *Caregiver:* demographic details, communication self-efficacy (adapted version of the Perceived Efficacy in Patient Physician Interactions Scale), quality of life (SF-36), preferences for information and involvement in decisions about patient care (adapted Degner Control Preference Scale, Cassileth Information Styles Questionnaire), achievement of preferences for information and involvement in decisions about care, understanding of participants' hopes for treatment, understanding of participants' preferences for future interventions, understanding of participants' prognosis, Quality of Death and Dying Scale.
Starting date	April 2010
Contact information	Prof Phyllis Butow Centre for Medical Psychology & Evidence-based Decision-making School of Psychology Brennan MacCallum Building (A18) University of Sydney NSW 2006 Australia E-mail: phyllis.butow@sydney.edu.au
Notes	Recruiting. Protocol published.

CTRI/2013/11/004128

Trial name or title	**A study to assess the feasibility of introducing early palliative care in ambulatory patients with advanced lung cancer**
Methods	Feasibility study
Participants	*Inclusion criteria:* • Patients with advanced lung cancer (stage IV) • ECOG Performance Status 0, 1, and 2 • Patients who can adhere to follow-up schedule at TATA Memorial Hospital • Age > 18 years • Written informed consent *Exclusion criteria:* • ECOG > 2 • Expected survival < 4 weeks
Interventions	*Experimental condition:* pain and symptom management and participant counselling; participants meet the palliative care team on the day of referral, then every month thereafter for 6 months
Outcomes	*Primary outcome measures:* More than 60% of referred patients have met the palliative care team; more than 50% of referred patients have completed the EORTC QLQ-30 and EORTC QLQ - LC13 (lung- cancer) and ESAS *Secondary outcome measures:* symptom burden (ESAS), quality of life (EORTC QLQ 30 and EORTC QLQ - LC13)
Starting date	September 2013
Contact information	Dr Jayita Deodhar Associate Professor Tata Memorial Hospital Dr. E. Borges Road Parel Mumbai Mumbai, Maharastra, 400012 India E-mail: jukd2000@yahoo.co.uk
Notes	Last updated on CTRI on 22 May 2017: "open to recruitment"

CTRI/2016/03/006693

Trial name or title	**Effect of early integration of specialized palliative care into standard oncologic treatment on the quality of life of patients with advanced head and neck cancers: a randomized controlled trial**
Methods	Randomised, parallel-group trial
Participants	*Inclusion criteria:*

CTRI/2016/03/006693 *(Continued)*

	• Patients with histologically confirmed squamous cell carcinoma of head and neck cancer in stage IV • ECOG 0, 1, and 2 • Planned for treatment with palliative intent • Age > 18 years • Understands Hindi, Marathi, or English • Willing to participate in follow-up *Exclusion criteria:* • Patients with surgically resectable tumours • Planned for definitive radiotherapy • Uncontrolled comorbidities, such as uncontrolled diabetes mellitus, uncontrolled hypertension • Already receiving care from palliative care services Target sample size is N = 180
Interventions	*Experimental condition:* early palliative care arm: Participant will receive specialist palliative care along with standard oncological treatment; participants in this arm will consult palliative care team along with parent oncology team; follow-up visit will be provided as per need; chemotherapeutic drugs will be given according to disease status as per institutional protocol *Control condition: s*tandard arm: Participants in this arm will receive standard oncological treatment; follow-up visits will be decided by the oncologist as per treatment protocol; chemotherapeutic drugs will be given according to disease status as per institutional protocol
Outcomes	*Primary outcome measures:* change in quality of life, measured by FACIT-H&N at 3 months after initial visit *Secondary outcome measures:* changes in symptom burden assessed by Edmonton Symptom Assessment Scale (ESAS-r) at 3 months after initial visit; overall survival at 3 months after initial visit
Starting date	March 2016
Contact information	M.A. Muckaden Room 132, Department of Palliative Medicine, Ground Floor, Main Building, Tata Memorial Hospital, Parel (E), Mumbai 400012 Mumbai, MAHARASHTRA India
Notes	Last updated on CTRI on 22 May 2017: "not yet recruiting"

DRKS00006162

Trial name or title	**Early palliative care – health services research and implementation of sustainable changes**
Methods	Feasibility study
Participants	Early palliative care services provided in this study are aimed at patients with advanced metastatic cancer that is unresponsive to curative treatments (ICD 10 C 1–80 + ICD 10 C 78–79). In all participating comprehensive cancer centres, patients will be identified by the tumour boards at each centre. As soon as the diagnostic process has been concluded and treatment has started (i.e. within the first 8 weeks after diagnosis), patients will be referred to the PC physician Target sample size is N = 2000
Interventions	In the main study phase, participants with metastatic cancer will routinely be offered a consultation with the palliative care physician within 8 weeks of diagnosis. This initial consultation has multiple objectives. First, this meeting serves to provide information regarding the value and accessi-

DRKS00006162 *(Continued)*

	bility of specialist palliative care. The palliative care physician will explain to participants that interdisciplinary cancer treatment ensures that all meaningful treatment options will continue to be available ("fight against cancer"), but that high priority will be placed on quality of life also. For quality of life needs, specialist palliative care services will be available to participants, alongside treatment from the primary cancer specialist
Outcomes	Early palliative care will be considered feasible if 75% of all eligible patients (i.e. adult patients with the diagnosis of an incurable, metastatic cancer [ICD 10 C 1–80 + ICD 10 C 78–79]) are referred to a palliative care physician at their centre at least once within 8 weeks of the initial diagnosis. Participants' quality of life and symptom burden will be assessed at the initial palliative care consultation on the POS, the EORTC QLQ-C30, and the HADS. In both preliminary and main study phases, follow-up assessment will be conducted at 12 and 24 weeks with these 3 instruments. Family/caregivers of the participant will be asked to assess the participant's situation by filling out the Quality of Dying and Death questionnaire.
Starting date	October 2014
Contact information	Dr Cornelia Meffert Department of Palliative Care, Comprehensive Cancer Center University Medical Center Freiburg Robert-Koch-Str. 3 79106 Freiburg Germany E-mail: cornelia.meffert@uniklinik-freiburg.de
Notes	Protocol published. Last updated on DRKS on 22 May 2017: "recruiting"

ISRCTN13337289

Trial name or title	**SPECIAL: Standard or palliative care in advanced lung cancer - does early referral of patients with metastatic non-small cell lung cancer to UK specialist palliative care services make a difference in their quality of life or survival?**
Methods	Phase III randomised controlled trial with integral feasibility stage (non-randomised)
Participants	*Inclusion criteria:* • Any adult (18 years or older) patient with newly diagnosed stage IV non-small cell lung cancer, with histologically confirmed diagnosis • ECOG performance score 0-3 *Exclusion criteria:* • ECOG performance score 4 • Prognosis of 2 weeks • Participation in another local competing supportive or palliative care study • Dementia, delirium, or other lack of capacity or communication that renders the patient unable to participate in the study • Any other psychological disorder that, in the view of the investigator, renders the patient unable to participate • Unable to communicate in English or with the help of an interpreter

ISRCTN13337289 *(Continued)*

Interventions	Arm A: standard of care (i.e. standard referral to specialised palliative care, if participant is willing) Arm B: sub-randomisation Arm B1: early specialised palliative care referral + standard of care Arm B2: early specialised palliative care referral + standard of care + Sheffield Profile for Assessment and Referral for Care assessment
Outcomes	*Primary outcome measures:* Global Health Status Score at 3 months after study entry, quality-adjusted survival time over 6 months *Secondary outcome measures:* overall survival, anxiety/depression, pain, health economics, quality of life, memory and cognitive ability, Modified Glasgow Prognostic Score
Starting date	September 2015
Contact information	Sam H. Ahmedzai c/o Trial Co-ordinator Cancer Research (UK) Clinical Trials Unit School of Cancer Sciences University of Birmingham Edgbaston B15 2TT Birmingham United Kingdom E-mail: special@trials.bham.ac.uk
Notes	Last updated on ISRCTN on 28 November 2016: "recruiting completed"

ISRCTN18955704

Trial name or title	**A multicentre non-blinded randomised controlled trial to assess the impact of regular early specialist symptom control treatment on quality of life in malignant mesothelioma (RESPECT-MESO)**
Methods	Multi-centre non-blinded, randomised controlled, parallel-group trial
Participants	*Inclusion criteria:* • Histological or cytological confirmation of malignant pleural mesothelioma • ECOG performance score of 0 to 1 • Diagnosis of malignant pleural mesothelioma received within the last 6 weeks • Ability to provide written informed consent in English and comply with trial procedures *Exclusion criteria:* • Other known malignancy within 5 years (excluding localised squamous cell carcinoma of the skin, cervical intraepithelial neoplasia, grade III, and low-grade prostate cancer (Gleason score < 5, with no metastases)) • Significant morbidity that the lead physician or multidisciplinary team feels will unduly confound or influence health-related quality of life • Patients the multi-disciplinary team judges require referral to specialist palliative care at the point of diagnosis

ISRCTN18955704 *(Continued)*

	• Concurrent, or within 3 months, participation in another clinical trial that may affect health-related quality of life • Referral at the time of recruitment for cytoreductive, tumour de-bulking, radical decortication or extrapleural pneumonectomy surgery for malignant pleural mesothelioma (video-assisted thoracoscopic surgery or 'mini' thoracotomy for pleurodesis and diagnosis attempts are permissible) • Chemotherapy treatment for malignant pleural mesothelioma initiated before consent • Significant history of depression/anxiety/psychiatric illness requiring specialist hospital care within the last 12 months Target sample size is N = 174
Interventions	*Experimental condition:* regular early SSCT: In the regular early SSCT group, participants will be seen within 3 weeks of randomisation by the specialised palliative care team (regardless of, and in addition to, all other treatments being offered). The initial meeting will consist of an approximately 1-hour consultation with a member of the specialist palliative care team. This may be a Consultant or Specialist Palliative Care Clinical Nurse Specialist. Participants then will continue to be seen regularly on at least a 4-weekly basis (regardless of other treatments, interventions, and symptoms) by a member of the specialist palliative care team, with consultations lasting approximately 30 minutes. These monthly reviews will continue until end of trial or participant death. *Control condition:* "standard therapy"
Outcomes	Primary outcome measures: global quality of life at 12 weeks post randomisation Secondary outcome measures: • Quality of life of participants after 24 weeks • Participant mood at 12 and 24 weeks • Primary caregiver quality of life and mood at 12 and 24 weeks, and at 24 weeks after participant death • Overall survival between study groups • Healthcare utilisation and healthcare costs • Cost-effectiveness of regular early SSCT when compared with usual practice Added 21/08/2014: • Subgroup analysis of health-related quality of life at 12 and 24 weeks for participants based on neutrophil, lymphocyte ratio, and radiological staging at time of diagnosis
Starting date	January 2014
Contact information	Portsmouth Hospitals NHS Trust Department of Respiratory Medicine Queen Alexandra Hospital Southwick Hill road Cosham Portsmouth PO6 3LY United Kingdom +44 (0)23 9228 6000 E-Mail: chief-investigator-ajc@respect-meso.org
Notes	Protocol published. Last updated on ISRCTN on 17 October 2016: "completed"

NCT01589328

Trial name or title	**Randomized controlled trials for the effect of early management on PAin and DEpression in patients with PancreatoBiliary cancer (EPADE-PB)**
Methods	RCT
Participants	*Inclusion criteria:* • Ages eligible for study: 18 years and older • Pathologically confirmed locally advanced or metastatic pancreatic cancer or biliary tract cancer • Within 8 weeks after diagnosis • Cancer-related pain (BPI worst pain score > 3), depression (CES-D > 16), or both • Karnofsky Performance Rating Scale ≥ 50% *Exclusion criteria:* • Opioid intolerance • History of drug or alcohol abuse • Impaired sensory or cognitive function • Pregnant and lactating women • Women of child-bearing potential not using a contraceptive method • Sexually active fertile men not using effective birth control during medication of study drug and up to 6 months after completion of study drug if their partners are women of child-bearing potential Target sample size is N = 288
Interventions	*Experimental condition:* early palliative care; interventions consisted of the following: nursing assessment of pain and depression mood; pain control-based NCCN guideline; depression control by psychoeducation and/or consultation of psychiatrist specialist; participant education *Control condition:* usual oncological care; participants randomly assigned to usual oncological care were not scheduled to meet with the palliative care service unless a meeting was requested by the participant, the family, or the oncologist; those who were referred to the service did not cross over to the early palliative care group or follow the specified palliative care protocol
Outcomes	*Primary outcome measures:* reduction in pain score (BPI) at 1 month and every 3 months up to 1 year; reduction in depression score (CES-D) at 1 month and every 3 months up to 1 year *Secondary outcome measures:* quality of life (EORTC QLQ-C30 General Questionnaire, Korean version) at baseline, at 1 month, and every 3 months up to 1 year; overall survival
Starting date	April 2012
Contact information	WooJin Lee, MD National Cancer Center Goyang, 410-769, Gyeonggi-do Republic of Korea E-mail: wsm@ncc.re.kr
Notes	Last updated on ClinicalTrials.gov on 3 October 2016: "This study is currently recruiting participants."

NCT01828775

Trial name or title	**Integration of palliative care for cancer patients on phase I trials**
Methods	RCT
Participants	*Inclusion criteria:* • Patients diagnosed with solid tumours who are eligible for participation in phase I clinical trials of investigational cancer therapies • Patients who have signed an informed consent for participation in phase I clinical trials • Able to read or understand English - this is included because the intervention and study materials (including outcome measures) are provided only in English • Ability to read and/or understand study protocol requirements and to provide written informed consent *Exclusion criteria:* • Patients with diagnosis of haematological (as a population distinct from solid tumours and different studies) or brain cancers (due to cognitive ability)
Interventions	*Experimental condition:* early PCI; participants receive part I of the PCI comprising quantitative surveys, comprehensive palliative care assessment by research nurses, and goals of care discussions beginning before administration of the first dose of phase I treatment; participants then receive part II of the PCI comprising recommendations from the interdisciplinary team, participant educational sessions, and supportive care referrals following the first dose of phase I treatment and completed within 1 month of the first treatment *Control condition:* delayed PCI; participants receive usual care until 12 weeks post treatment initiation; participants then receive both part I and part II of the PCI
Outcomes	*Primary outcome measures:* change in overall quality of life scores (FACT-G and FACIT-Sp) at 12 weeks; change in psychological distress (NCCN Distress Thermometer) at 12 weeks; satisfaction with communication (FAMCARE) at 12 weeks; participants' symptom intensity and symptom interference with daily activities (Psychological Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events) at 4 and 12 weeks; total numbers of supportive care referrals (social work, dietician, chaplaincy, psychologist/psychiatrist) at 12 weeks; total numbers of unscheduled outpatient encounters and inpatient admissions at 12 weeks; total number of hospice referrals at 12 weeks; retention in the phase I trial at 12 weeks; participant satisfaction with the PCI at 12 weeks
Starting date	September 2014
Contact information	Betty Ferrell, PhD, MA, FAAN, FPCN City of Hope - Main Campus (Duarte) 1500 East Duarte Road Duarte, CA 91010 United States E-mail: bferrell@coh.org
Notes	Last updated on ClinicalTrials.gov on 31 May 2017: "This study is currently recruiting participants."

NCT01865396

Trial name or title	**Effect of early palliative care on quality of life of patients with advanced cancer: a randomised controlled trial**

NCT01865396 *(Continued)*

Methods	RCT
Participants	*Inclusion criteria:* Patients with life-limiting cancer (prognosis of approximately 1 year) are eligible if: • they are within 12 weeks of referral from another hospital after receiving first-line treatment or within 8 to 12 weeks of a new diagnosis (histologically and cytologically confirmed): metastatic and advanced pancreatic, stomach, oesophageal, and biliary tract adenocarcinoma; metastatic or advanced NSCLC (stage IIIB or IV) or metastatic SCLC, malignant pleural mesothelioma, metastatic or advanced head and neck cancer (stage III or IV) • they are within 12 weeks of progression after receiving treatment and have a prognosis of approximately 1 year: metastatic and locally advanced colorectal cancer, with progression after second-line treatment; metastatic or advanced prostate carcinoma after second-line treatment, advanced breast cancer with visceral and/or brain metastasis, with progression on second- or third-line treatment; metastatic melanoma, metastatic or advanced kidney cancer, metastatic or advanced bladder cancer after first-line treatment • an ECOG performance status of 0, 1, or 2 and ability to read and respond to questions in Dutch *Exclusion criteria:* • Patients < 18 years old • Patients with impaired cognition • Patients who met the palliative support team more than once or had a consultation within 6 months of inclusion Target sample size is N = 186
Interventions	*Experimental condition:* early palliative care; interventional palliative care after diagnosis and once a month *Control condition:* standard care; participants will receive standard oncological care
Outcomes	*Primary outcome measures:* quality of life of the participant and his or her family caregiver at baseline, at 12 weeks, and 6-weekly after 12 weeks (EORTC-QLQ C30, McGill QOL, SF-36) *Secondary outcome measures:* influence of palliative care on mood and illness understanding of participants and family caregivers at baseline, at 12 weeks, and 6-weekly after 12 weeks (HADS, PHQ-9, illness understanding), influence of palliative care on decisions of physicians with regards to end-of-life care (questionnaire for decisions with regards to end-of-life decision making for physicians)
Starting date	April 2013
Contact information	Gaëlle Vanbutsele, MSc, Clinical Psychologist Doctoral Researcher End-of-Life Care Research Group Vrije Universiteit Brussel & Ghent University UZ Gent De Pintelaan 185, 9000 Gent Belgium E-mail: gaelle.vanbutsele@vub.ac.be
Notes	Abstract published. Last updated on ClinicalTrials.gov on 1 July 2016: "This study is ongoing, but not recruiting participants."

NCT01885884

Trial name or title	**A pilot trial of an embedded collaborative model of supportive care for pancreatic cancer**
Methods	RCT
Participants	*Inclusion criteria:* • Patients: adults (≥ 18 years old), pathologically confirmed locally advanced or metastatic pancreatic adenocarcinoma diagnosed within the past 8 weeks, ECOG Performance Status of 0 (asymptomatic), 1 (symptomatic but fully ambulatory), or 2 (symptomatic and in bed < 50% of the day), planning to receive continued care from an oncologist at the Hillman Cancer Center, accompanied by a caregiver (family member or friend) at the first visit • Caregivers: adults (≥ 18 years old), family member or friend of an eligible patient *Exclusion criteria:* • Patients: unable to read and respond to questions in English, not planning to receive continued care from an oncologist at the Hillman Cancer Center Pancreatic, neuroendocrine cancer • Caregivers: unable to read and respond to questions in English Target sample size is N = 60
Interventions	*Experimental condition:* supportive care intervention; monthly (minimum) participant and caregiver visits with a supportive care physician, embedded within their standard oncological care (through collaboration with oncology providers) *Control condition:* usual care; participants will receive standard oncology care from their oncology providers
Outcomes	*Primary outcome measures:* trial feasibility; acceptability of intervention participation at 3 months (+/- 3 weeks); perceived effectiveness at 3 months (+/- 3 weeks) *Secondary outcome measures:* change in participant quality of life (FACT-Hep) at 3 months (+/- 3 weeks); participant healthcare utilisation (numbers and types of chemotherapy regimens, frequency and timing of chemotherapy regimens, number and length (days) of hospital admissions, number and length (days) of intensive care unit admissions, number of emergency department visits, frequency and timing (days before death) of hospice use, place of death)
Starting date	July 2013
Contact information	Yael Schenker, MD, MAS Assistant Professor of Medicine University of Pittsburgh Cancer Institute (UPCI) Hillman Cancer Center Pittsburgh, Pennsylvania, 15232 United States E-mail: schenkery@upmc.edu
Notes	Last updated on ClinicalTrials.gov on 10 May 2016: "This study has been completed."

NCT01983956

Trial name or title	**A structured early palliative care intervention for patients with advanced cancer - a randomized controlled trial with a nested qualitative study (SENS trial)**
Methods	RCT
Participants	*Inclusion criteria:* • Diagnosed within the last 16 weeks • Metastatic or locally advanced, not amenable to curative treatment, NSCLC, or • Metastatic or locally advanced, not amenable to curative treatment, colorectal cancer, or • Metastatic or locally advanced, not amenable to curative treatment, prostate cancer, or • Metastatic or locally advanced, not amenable to curative treatment, breast cancer with visceral and/or brain metastasis, or • Metastatic or locally advanced, not amenable to curative treatment, bladder/urothelium cancer, or • Metastatic or locally advanced, not amenable to curative treatment, pancreatic cancer • Diagnosis histologically confirmed • ECOG Performance Status of 0, 1, or 2 • At least 18 years of age at the time of enrolment • Signed informed consent with understanding of study procedures and the investigational nature of the study *Exclusion criteria:* • Presence of delirium or dementia or other reason for lack of ability to give informed consent • Inability to communicate adequately in German • Lack of patient accountability; inability to appreciate the nature, meaning, and consequences of the study and to formulate his or her own wishes correspondingly • Patients already receiving care from an inpatient palliative care service Target sample size is N = 150
Interventions	*Experimental condition:* structured approach intervention with the SENS model based on the bio-psycho-social-spiritual model of care and WHO definitions of palliative care, as well as NCCN Practice Guidelines for Palliative Care. It supports assessment of areas and complexity of concerns from the participant perspective, determines the priority and structures the support needed. Intervention is provided by palliative care physicians and nurses collaboratively. It is utilised as baseline assessment and afterwards is integrated into each routine oncology care outpatient and inpatient visit. Depending on the goals, it may be applied between routine visits. In addition, participants will receive usual oncology care throughout the study period *Control condition:* Participants in the usual care group will receive routine oncology care throughout the study. This incorporates a routine assessment according to the standard Swiss Group for Clinical Cancer Research (SAKK) protocol, which assesses overall symptoms. Participants are not seen by nurses during a routine visit to the outpatient clinic unless they need a blood withdrawal or any intravenous or subcutaneous treatment. Only nursing staff in the palliative care unit is familiar with using the SENS-assessment instrument. Participants assigned to usual care may meet with the palliative care service on request according to established practice
Outcomes	*Primary outcome measures:* distress over 6 months (NCCN Distress Thermometer) *Secondary outcome measures:* quality of life (FACT-G) at 6 months; POS at 6 months; overall survival; location of death; healthcare utilisation (questionnaire of Stanford Patient Education Research Centre)
Starting date	December 2013
Contact information	Steffen Eychmueller, MD

NCT01983956 *(Continued)*

	University Center for Palliative Care Bern University Hospital SWAN Haus Freiburgstrasse 28 CH-3010 Bern Switzerland E-mail: steffen.eychmueller@insel.ch
Notes	Last updated on ClinicalTrials.gov on 27 September 2016: "This study is currently recruiting participants."

NCT02308865

Trial name or title	**Impact of early palliative care on quality of life and survival of patients with non-small-cell metastatic lung cancer in Northern France**
Methods	RCT
Participants	*Inclusion criteria:* • Diagnosis of non-small cell lung cancer, proven histologically, metastatic proven imaging (MRI, CT scanner, PET scan), stage IV (any T, any N, M1), diagnosed in the 8 weeks preceding inclusion, supported outpatient • Age > 18 years • PS ≤ 2 • Patient able to understand the nature, purpose, and methods of the study • Signed Informed consent *Exclusion criteria:* • Age < 18 years • Patient already supported by palliative care • Patient with an activating EGFR mutation or EML4-ALK rearrangement • Patient under trusteeship/guardianship Target sample size is N = 144
Interventions	*Experimental condition:* multidisciplinary palliative care monthly consultations with a doctor, a nurse, a psychologist, and possibility a physical therapist and a chaplain, in addition to standard onco-pneumological care *Control condition:* participant supported by the oncological respiratory service for treatment of disease by chemotherapy and for treatment of complications
Outcomes	*Primary outcome measures:* quality of life (Trial Outcome Index) at 12 weeks *Secondary outcome measures:* survival; events (presence of any of the following: chemotherapy, use of resuscitation, or no treatment, limiting decision 14 days before death); quality of life (FACT-L, PHQ-9, and HADS questionnaires) at 12 and 21 weeks
Starting date	October 2014
Contact information	Licia Touzet, MD

NCT02308865 *(Continued)*

	University Hospital Lille 59000 Lille France E-mail: licia.touzet@chru-lille.fr
Notes	Last updated on ClinicalTrials.gov on 18 May 2017: "This study is currently recruiting participants."

NCT02332317

Trial name or title	**A randomized, controlled phase III study of integrated, specialized palliative rehabilitation for patients with newly diagnosed non-resectable cancer**
Methods	RCT
Participants	*Inclusion criteria:* Participants must: • receive a diagnosis of non-resectable cancer less than 8 weeks before inclusion • be fit to receive standard oncology treatment and to accept treatment • read and understand Danish • sign informed consent *Exclusion criteria:* • Contact with a specialised palliative unit within the last year before inclusion • Inability to co-operate during the study • Missing informed consent Target sample size is N = 300
Interventions	*Experimental condition:* 150 participants will receive standard oncology treatment alongside a 12-week specialised palliative rehabilitation programme *Control condition:* 150 participants will receive standard oncology treatment
Outcomes	*Primary outcome measures:* effect of the intervention on "The Primary Problem" chosen by the participant (EORTC-QLQ-C30 that correlates with "the primary problem" of the participant) at 6 and 12 weeks *Secondary outcome measures:* EORTC-QLQ-C30 at 6 and 12 weeks; worries and symptoms of anxiety and depression (HADS) at 6 and 12 weeks; all-cause mortality; economic consequences
Starting date	November 2014
Contact information	Lars Henrik Jensen, MD, PhD Department of Oncology VejleHospital DK-7100 Vejle Denmark E-mail: Lars.Henrik.Jensen@rsyd.dk

NCT02332317 *(Continued)*

Notes	Last updated on ClinicalTrials.gov on 31 May 2017: "This study is currently recruiting participants."

NCT02335619

Trial name or title	**Early integrated supportive care study for gastrointestinal cancer patients**
Methods	RCT
Participants	*Inclusion criteria:* • Diagnosis of gastrointestinal cancer • Appointments in gastronintestinal clinic during study days • Ability to complete a symptom assessment form alone or with the help of a family member or interpreter *Exclusion criteria:* • Already receiving care from the Pain and Symptom Management/Palliative care team Target sample size is N = 152
Interventions	*Experimental condition:* early palliative care; during first oncology appointment, participants in the intervention arm will self-report to the study team any symptoms related to their cancer or treatment; scores at or above a defined benchmark will be seen by Pain and Symptom Management/Palliative Care team members during or immediately after their oncology appointment; participants will be asked to self-report symptoms once a month following recruitment for 4 months *Control condition:* standard care; during first oncology appointment, participants in the control arm will self-report to the study team any symptoms related to their cancer or treatment; self-reports will be collected but will not be shared with the Pain and Symptom Management/Palliative Care Team, and participants will continue with their oncology appointment as per standard procedure; participants will be asked to self-report symptoms once a month following recruitment for 4 months
Outcomes	*Primary outcome measure:* total symptom distress score at 4 months after recruitment (modified ESAS) *Secondary outcome measures:* use of health services at 4 months after recruitment (number of hospital admissions for non-treatment reasons; number of emergency room visits; number of referrals to the Pain and Symptom Management/Palliative Care Team; number of Pain and Symptom Management/Palliative Care follow-up visits per participant); aggressiveness of cancer treatment; details of death
Starting date	February 2015
Contact information	Pippa Hawley, MD Head Palliative Care Physician British Columbia Cancer Agency Vancouver, British Columbia, V5Z 4E6 Canada E-mail: phawley@bccancer.bc.ca

NCT02335619 *(Continued)*

Notes	Last updated on ClinicalTrials.gov on 14 April 2015: "The recruitment status of this study is unknown. The completion date has passed and the status has not been verified in more than two years."

NCT02349412

Trial name or title	
Methods	
Participants	
Interventions	The study intervention consists of early integration of palliative care services into standard oncology care provided in an outpatient setting for participants with advanced lung and non-colorectal gastrointestinal malignancies who are not being treated with curative intent. Palliative care services provided to participants randomised to the intervention will be provided by board-certified physicians and/or advanced practice nurses and will focus on the following areas: developing and maintaining the therapeutic relationship with participants and family caregivers; assessing and treating participant symptoms; providing support and reinforcement for coping with advanced cancer among participants and family caregivers; assessing and enhancing prognostic awareness and illness understanding in participants and family caregivers; assisting with treatment decision making; and (6) assisting with end-of-life care planning
Outcomes	*Primary outcome measure:* change in FACT-G scores from baseline to 12 weeks *Secondary outcome measures:* change in quality of life on FACT-G over time, depressive symptoms as per HADS, rate of anxiety symptoms as per HADS at 12 weeks and over time, change in illness understanding over time, change in quality of life on the SF-36 over time, rate of referral, enrolment and length of stay in hospice, location of death, number of hospital and intensive care unit admissions and days, chemotherapy and radiation administration, overall survival, concordance between participant and family caregiver report of prognosis/curability
Starting date	April 2015
Contact information	Jennifer S. Temel, MD Massachusetts General Hospital, 55 Fruit St. Yawkey 7B, Boston, MA 02114 United States E-mail: jtemel@partners.org
Notes	Last updated on ClinicalTrials.gov on 19 April 2017: "This study is ongoing, but not recruiting participants."

NCT02547142

Trial name or title	**Evaluation of the implementation of an early integrated palliative care program in the esophageal cancer population**
Methods	RCT
Participants	*Inclusion criteria:*

NCT02547142 *(Continued)*

	• Patients newly diagnosed or referred to the Esophageal Diagnostic Assessment Program with suspicious findings found to be oesophageal cancer • Patients who present with metastatic disease, defined as N3 lymph node involvement or distant metastatic deposits as confirmed on PET scan • Patients must have been notified by a member of their healthcare team of their prognosis and palliative categorisation, as noted in the patient chart, within 8 weeks of diagnosis • Patients may undergo oesophagectomy, stenting, brachytherapy, or palliative intent chemotherapy or radiotherapy as clinically indicated *Exclusion criteria:* • Individuals unable to complete questionnaires with assistance • Patients presently undergoing neoadjuvant chemotherapy or radiotherapy for malignancy • Patients with recurrent oesophageal cancer • Patients who are referred back to the Esophageal Diagnostic Assessment Program for restaging after completing neoadjuvant therapy Target sample size is N = 700
Interventions	Early palliative care (not further specified)
Outcomes	*Primary outcome measure:* quality of life *Secondary outcome measures:* oesophageal cancer-specific symptom score FACT-E, PHQ-9, HADS, participant survival post metastatic oesophageal cancer diagnosis
Starting date	October 2015
Contact information	Christian J Finley, MD, MPH, FRCSC McMaster University 50 Charlton Avenue East, T-2105 Hamilton, Ontario L8N 4A6 Canada E-mail: finleyc@mcmaster.ca
Notes	Last updated on ClinicalTrials.gov on 15 March 2016: "This study is currently recruiting participants."

NCT02631811

Trial name or title	**Early palliative care in patients with acute leukaemia (Pablo Hemato)**
Methods	RCT
Participants	*Inclusion criteria:* • > 18 years old • Acute lymphoblastic or myeloblastic leukaemia at first relapse and diagnosed within 8 weeks before inclusion • Patients for whom a curative strategy (transplant) is not considered • Patients older than 75 years at diagnosis • Informed signed consent *Exclusion criteria:*

NCT02631811 *(Continued)*

	• Inability to complete the questionnaire • Psychiatric disorders other than depression • Persons under guardianship Target sample size is N = 40
Interventions	*Experimental condition:* Participants will be seen by palliative care team at least once a month until the 12th week, more often if needed. Symptoms and suffering will be assessed by a multi-disciplinary palliative specialist team of physician, nurse, and psychologist. Physical, psychological, social, and existential suffering will be addressed *Control condition:* "usual medical follow-up"
Outcomes	*Primary outcome measure:* • Measure of quality of life [time frame: 12 weeks] [designated as safety issue: no] - quality of life measured by FACT-Leu questionnaire. Score for quality of life will be compared between groups *Secondary outcome measures:* • Measure of symptom intensity [time frame: 12 weeks] [designated as safety issue: no] • Symptom intensity measured by ESAS questionnaire. Score for symptom intensity will be compared between groups • Measure of depression [time frame: 12 weeks] [designated as safety issue: no] - score of depression measured by HADS questionnaire. Score of depression will be compared between groups • Measure of anxiety [time frame: 12 weeks] [designated as safety issue: no] - score of anxiety measured by HADS questionnaire. Score of anxiety will be compared between groups • Measure of quality of the end of life [time frame: up to 9 months] [designated as safety issue: no] - within the last month of life, several parameters will be studied to evaluate the quality of the end of life, such as number of admissions in the emergency unit • Overall survival [time frame: 9 months] [designated as safety issue: yes]
Starting date	November 2015
Contact information	Marilène FILBET, PU-PH Centre Hospitalier Lyon Sud Pierre Bénite, France, 69495 E-Mail: marilene.filbet@chu-lyon.fr
Notes	Last updated on ClinicalTrials.gov on 11 December 2015: "This study is currently recruiting participants."

NCT02712229

Trial name or title	**A primary palliative care intervention for patients with advanced cancer (CONNECT)**
Methods	Cluster-randomised controlled trial (cRCT)
Participants	*Inclusion criteria:* Participants will be patients with advanced cancer receiving care at a participating clinic; their caregivers; their oncology staff nurses, oncologists, and practice managers. They will be adults (≥ 21 years old); with metastatic solid tumours; the oncologist "would not be surprised if the patient died in the next year"; Eastern Cooperative Oncology Group performance status (ECOG PS)

NCT02712229 *(Continued)*

	≤ 2; planning to receive ongoing care from a participating oncologist and willing to be seen at least monthly *Exclusion criteria:* Inability to read and respond to questions in English; cognitive impairment or inability to consent to treatment, as determined by the patient's oncologist; inability to complete baseline interview; ECOG PS of 3 (capable of limited self-care; confined to bed or chair > 50% of waking hours) or 4 (cannot carry on any self-care; totally confined to bed or chair); haematological malignancy Target sample size is N = 1486
Interventions	*Experimental condition:* CONNECT CONNECT is a primary palliative care - care management intervention led by existing oncology nurses. CONNECT is deployed through a series of nurse-led encounters occurring before or after regularly scheduled oncology clinic visits. Based on best practices in palliative oncology care, the first visit focusses on establishing rapport, addressing symptom needs, and choosing a surrogate decision maker. Subsequent visits include additional focus on treatment preferences and future goals. CONNECT visits are guided by participant-reported outcomes. During every CONNECT encounter, the nurse will work with participants and caregivers to complete and update individualized shared care plans. After every CONNECT visit, the nurse will discuss participants' symptoms, preferences, and goals with their oncologists via a mandatory check-in session and will conduct a follow-up call with the participant and/or caregiver. *Control condition:* Usual care control. At clinics randomised to usual care, enrolled participants and caregivers will continue to receive supportive oncology care according to usual practice.
Outcomes	*Primary outcome measure:* • Quality of life - participant [time frame: change from baseline to 3 months] [designated as safety issue: no] - investigators will compare change in 3-month FACIT-Pal scores between enrolled participants at intervention clinics and enrolled participants at usual care clinics *Secondary outcome measures:* • Symptom burden - participant [time frame: change from baseline to 3 months] [designated as safety issue: no] - investigators will compare change in 3-month ESAS scores between enrolled participants at intervention clinics and enrolled participants at usual care clinics • Depression and anxiety symptoms - participant [time frame: change from baseline to 3 months] [designated as safety issue: no] - investigators will compare change in 3-month HADS scores between enrolled participants at intervention clinics and enrolled participants at usual care clinics • Depression and anxiety symptoms - caregiver [time frame: change from baseline to 3 months] [designated as safety issue: no] - investigators will compare change in 3-month HADS scores between enrolled caregivers at intervention clinics and enrolled caregivers at usual care clinics • Caregiver burden - caregiver [time frame: change from baseline to 3 months] [designated as safety issue: no] - investigators will compare change in 3-month Zarit Burden Interview-Short scores between enrolled caregivers at intervention clinics and enrolled caregivers at usual care clinics • Healthcare utilisation [time frame: 1 year] [designated as safety issue: no] - to inform future dissemination efforts and aid in understanding of optimal financing models, investigators will calculate implementation costs of the intervention and will determine the effects of CONNECT on healthcare utilisation, including hospitalisations, chemotherapy use, and hospice use • Survival - participants [time frame: 1 year] [designated as safety issue: no] - investigators will calculate survival time from date of enrolment using the Kaplan-Meier method. We will use frailty models to assess for any effect of CONNECT on survival, while controlling for effects of clustering.
Starting date	April 2016
Contact information	Yael Schenker, MD, MAS Assistant Professor of Medicine

NCT02712229 *(Continued)*

	University of Pittsburgh Cancer Institute (UPCI) Hillman Cancer Center Pittsburgh, Pennsylvania, 15232 United States E-mail: schenkery@upmc.edu
Notes	Last updated on ClinicalTrials.gov on 7 December 2016: "This study is currently recruiting participants."

NCT02730858

Trial name or title	Palliative and oncology care model In breast cancer
Methods	RCT
Participants	*Inclusion criteria:* • Metastatic breast cancer • Diagnosis of any of the following within the prior 4 weeks: leptomeningeal disease; progressive brain metastases after initial radiation therapy; triple negative breast cancer with progressive disease on first-line chemotherapy; or currently admitted to the hospital or admitted to the hospital within the prior 4 weeks • Receiving cancer care at Massachusetts General Hospital Cancer Center • Ability to read and write in English • ECOG status between 0 and 2 *Exclusion criteria:* • Already receiving palliative care in the outpatient setting • Active, untreated, unstable, serious mental illness (e.g. active, untreated psychotic, bipolar, or substance-dependence disorder) interfering with ability to participate • Cognitive impairment (e.g. delirium, dementia) interfering with ability to participate • Requires urgent palliative or hospice care Target sample size is N = 120
Interventions	*Experimental condition:* Participants randomised to the intervention will receive collaborative care from palliative care and oncology for the remainder of their illness. The initial 5 visits with palliative care will be conducted in accordance with study-specific clinical practice guidelines and will occur at least monthly *Control condition:* Participants randomised to oncology care alone will continue to receive routine care identical to what they would have received if they had not participated in the trial. Participants or their oncologists can request palliative care consultation at any point in time
Outcomes	*Primary outcome measure:* • End-of-life care preference documentation [time frame: 1 year] [designated as safety issue: no] - compare differences in rate of documentation of end-of-life care preferences (Yes documented vs No) *Secondary outcome measures:* • Participant-reported end-of-life care conversation [time frame: 6 months] [designated as safety issue: no] - examine participant report of end-of-life care preferences with the clinician using the

NCT02730858 *(Continued)*

	following item: "Have you and your doctors discussed any particular wishes you have about the care you want to receive if you were dying?" Although participants complete this measure repeatedly during the course of the study, investigators will use the final assessment before death or at 6 months' follow-up (whichever comes first) for this analysis • Participant-reported quality of life (FACT-Breast) [time frame: weeks 6, 12, 18, and 24] [designated as safety issue: no] - compare participant-reported quality of life between study arms at weeks 6, 12, 18, and 24 • Participant-reported depression symptoms (HADS) [time frame: weeks 6, 12, 18, and 24] [designated as safety issue: no] - compare participant-reported depression symptoms between study arms at weeks 6, 12, 18, and 24 • Participant-reported anxiety symptoms (HADS) [time frame: weeks 6, 12, 18, and 24] [designated as safety issue: no - compare participant-reported anxiety symptoms between study arms at weeks 6, 12, 18, and 24 • Chemotherapy at end of life [time frame: 14, 7 and 3 days before death] [designated as safety issue: no] - examine differences in rates of chemotherapy administration during the last 3, 7, and 14 days of life between study arms • Rate of hospice utilisation at end of life [time frame: 6 months] [designated as safety issue: no] - examine differences in rates of hospice utilisation between study arms • Length of stay in hospice [time frame: 6 months] [designated as safety issue: no] - examine differences in hospice length of stay between stud
Starting date	May 2016
Contact information	Jennifer Temel, MD Massachusetts General Hospital Bosten, Massachusetts, United States, 02115 E-Mail: jtemel@partners.org
Notes	Last updated on ClinicalTrials.gov on 15 April 2017: "This study is currently recruiting participants."

NCT02853474

Trial name or title	**Early palliative care in patients with metastatic upper gastrointestinal cancers treated with first-line chemotherapy (EPIC-1511)**
Methods	RCT
Participants	*Inclusion criteria:* • Patients with an upper gastrointestinal metastatic cancer: pancreatic, biliary tract, or gastric (including junctional Siewert 2 and 3 cancers) cancers. NB: Gastroesophageal junctional cancers with dysphagia and/or gastric/gastroesophageal cancers with unknown or positive HER2 status are not eligible • Patients planning to be treated with first-line chemotherapy for metastatic disease • Age ≥ 18 years • Life expectancy ≥ 1 month • Performance status (ECOG) ≤ 2 • Good understanding of French language • Signed and dated informed consent • Patients covered by government health insurance *Exclusion criteria:*

NCT02853474 *(Continued)*

- Locally advanced cancer
- Junctional Siewert 1 gastroesophageal cancer
- Gastric or junctional gastroesophageal cancer with dysphagia
- Gastric or junctional gastroesophageal cancer with unknown or positive HER2 status (IHC: +++ or IHC ++ and FISH/SISH +)
- Direct bilirubin > 2 ULN

Target sample size is N = 558

Interventions	*Sham comparator:* Arm A: chemotherapy alone. The medical oncologists (or gastroenterologist physicians) are in charge of the participant for chemotherapy administration, and for management of symptoms related to the disease and/or the treatment, in accordance with professional practices. If needed (at any time), a palliative consultation visit could be performed. Interventions include the EORTC-QLQ-C30 questionnaire for assessment of quality of life and HADS score for anxiety and depression assessment *Experimental:* Arm B: chemotherapy + early palliative care. Standard oncology care as for arm A plus early palliative consultation visits. Interventions include EORTC-QLQ-C30 questionnaire for assessment of quality of life and HADS score for anxiety and depression assessment. Early palliative care visits: A palliative consultation visit is a visit done by a palliative care physician. Any visits done by other professionals ARE NOT palliative consultation visits. Five palliative consultation visits are scheduled in this arm
Outcomes	*Primary outcome measure:* • Overall survival (as intent-to treat analysis) [time frame: average of 1 year] [designated as safety issue: no] - overall survival is defined as time between date of randomisation and date of death, whatever the cause *Secondary outcome measures:* • Overall survival (per-protocol analysis) [time frame: average of 1 year] [designated as safety issue: no] - overall survival curves in per-protocol analysis will be given • One-year survival rate (intent-to-treat and per-protocol analyses) [time frame: 1 year] [designated as safety issue: no] - 1-year survival rates with 95% confidence interval in both intent-to-treat and per-protocol analyses • Quality of life [time frame: every 8 weeks until participant withdrawal from the study (during an average of 1 year)] designated as safety issue: no] - quality of life is assessed with the EORTC QLQ-C30 questionnaire at baseline and, after inclusion, every 8 weeks until participant withdrawal from the study • Depression assessed with HADS score [time frame: every 8 weeks during 24 weeks] [designated as safety issue: no] - depression is assessed with the HADS (Hospital Anxiety and Depression Scale) at baseline and, after inclusion, every 8 weeks during 24 weeks. TUDD (time until definitive deterioration) [time frame: average of 1 year] [designated as safety issue: no] • TUDD for quality of life scores was defined as the time from randomisation to the first observation of definitive deterioration of EORTC QLQ-C30 score, or death. • Presence or lack of advanced directives [time frame: through study completion, an average of 1 year] [designated as safety issue: no] - number of participants for whom advanced directives are written in their medical records will be recorded • Questionnaire on "content of palliative care visits" [time frame: during the 6 first months after randomisation] [designated as safety issue: no] - a palliative care visit is a visit done by a palliative care physician. Any type of visit done by other professionals (i.e. dieticians, nurses, social workers, psychologists, pain specialists, etc.) IS NOT a palliative care visit. In Arm B (interventional arm), the content of each palliative care visit will be described by the palliative care physician at the end of the visit, by filling in a specific checklist built by an ad hoc working group of palliative care physicians • Number of participants treated with chemotherapy [time frame: 30 days before death of the participant] [designated as safety issue: no] - number of participants treated with chemotherapy in their 30 last days before death will be recorded

NCT02853474 *(Continued)*

Starting date	August 2016
Contact information	Ariette Da Silva, MD Antoine Adenis, MD, PhD Centre Oscar Lambret 3 Rue Frédéric Combemale, 59000 Lille, France E-Mail: a-dasilva@o-lambret.fr
Notes	Last updated on ClinicalTrials.gov on 10 January 2017: "This study is currently recruiting participants."

BPI: Brief Pain Inventory
CES-D: Center for Epidemiological Studies-Depression Scale
ECOG: Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
ESAS: Edmonton Symptom Assessment System
FACIT-Pal: Functional Assessment of Chronic Illness Therapy - Palliative Care
FACIT-Sp: Functional Assessment of Chronic Illness Therapy - Spirituality
FACT-Breast: Functional Assessment of Cancer Therapy - Breast
FACT-E: Functional Assessment of Cancer Therapy - Esophagus
FACT-G: Functional Assessment of Cancer Therapy - General
FACT-Hep: Functional Assessment of Cancer Therapy - Hepatobiliary
FACT-H&N: Functional Assessment of Cancer Therapy - Head and Neck
FACT-Leu: Functional Assessment of Cancer Therapy – Leukemia
FAMCARE: Family Satisfaction with Advanced Cancer Care Questionnaire
HADS: Hospital Anxiety and Depression Scale
NCCN: National Comprehensive Cancer Network
NSCLC: non-small cell lung cancer
PCI: palliative care intervention
PHQ-9: Patient Health Questionnaire
RCT: randomised controlled trial
SSCT: specialist symptom control treatment
SF-36: Short Form (36) Health Survey

DATA AND ANALYSES

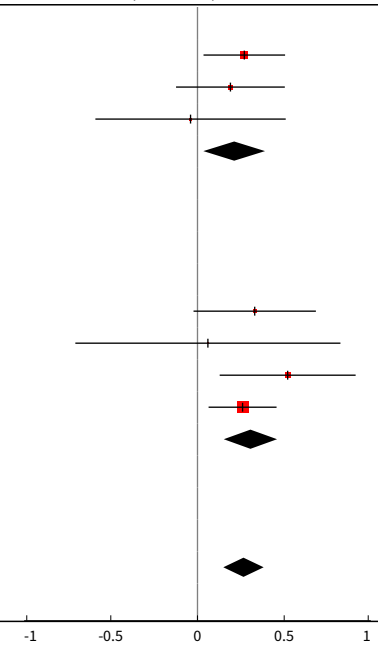
Comparison 1. Early palliative care vs standard oncological care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Health-related quality of life	7	1028	Std. Mean Difference (Random, 95% CI)	0.27 [0.15, 0.38]
1.1 Co-ordinated care model	3	485	Std. Mean Difference (Random, 95% CI)	0.21 [0.03, 0.39]
1.2 Integrated care model	4	543	Std. Mean Difference (Random, 95% CI)	0.31 [0.15, 0.46]
2 Depression	5	762	Std. Mean Difference (Random, 95% CI)	-0.11 [-0.26, 0.03]

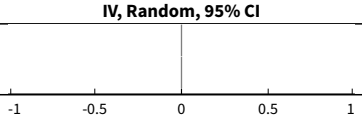
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Co-ordinated care model	3	526	Std. Mean Difference (Random, 95% CI)	-0.06 [-0.23, 0.12]
2.2 Integrated care model	2	236	Std. Mean Difference (Random, 95% CI)	-0.24 [-0.50, 0.02]
3 Survival	4	800	Hazard Ratio (Random, 95% CI)	0.85 [0.56, 1.28]
4 Symptom intensity	7	1054	Std. Mean Difference (Random, 95% CI)	-0.23 [-0.35, -0.10]
4.1 Co-ordinated care model	3	492	Std. Mean Difference (Random, 95% CI)	-0.23 [-0.41, -0.04]
4.2 Integrated care model	4	562	Std. Mean Difference (Random, 95% CI)	-0.23 [-0.43, -0.04]
5 Health-related quality of life (sensitivity analysis for study design including RCTs only)	5	696	Std. Mean Difference (Random, 95% CI)	0.29 [0.14, 0.44]
6 Symptom intensity (sensitivity analysis for study design including RCTs only)	5	696	Std. Mean Difference (Random, 95% CI)	-0.28 [-0.43, -0.13]

Analysis 1.1. Comparison 1 Early palliative care vs standard oncological care, Outcome 1 Health-related quality of life.

Study or subgroup	EPC N	TAU N	Std. Mean Difference (SE)	Std. Mean Difference IV, Random, 95% CI	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Co-ordinated care model						
Bakitas 2009	145	134	0.3 (0.12)		24.48%	0.27[0.03,0.51]
Bakitas 2015	72	83	0.2 (0.16)		13.77%	0.19[-0.12,0.5]
McCorkle 2015	23	28	-0 (0.28)		4.5%	-0.04[-0.59,0.51]
Subtotal (95% CI)					**42.74%**	**0.21[0.03,0.39]**
Heterogeneity: Tau²=0; Chi²=1.06, df=2(P=0.59); I²=0%						
Test for overall effect: Z=2.33(P=0.02)						
1.1.2 Integrated care model						
Maltoni 2016	64	65	0.3 (0.18)		10.88%	0.33[-0.02,0.68]
Tattersall 2014	13	13	0.1 (0.39)		2.32%	0.06[-0.7,0.82]
Temel 2010	60	47	0.5 (0.2)		8.81%	0.52[0.13,0.91]
Zimmermann 2014	140	141	0.3 (0.1)		35.25%	0.26[0.06,0.46]
Subtotal (95% CI)					**57.26%**	**0.31[0.15,0.46]**
Heterogeneity: Tau²=0; Chi²=1.77, df=3(P=0.62); I²=0%						
Test for overall effect: Z=3.89(P=0)						
Total (95% CI)					**100%**	**0.27[0.15,0.38]**
Heterogeneity: Tau²=0; Chi²=3.44, df=6(P=0.75); I²=0%						



Study or subgroup	EPC	TAU	Std. Mean Difference	Std. Mean Difference	Weight	Std. Mean Difference
	N	N	(SE)	IV, Random, 95% CI		IV, Random, 95% CI
Test for overall effect: Z=4.47(P<0.0001)						
Test for subgroup differences: Chi²=0.61, df=1 (P=0.44), I²=0%						



Analysis 1.2. Comparison 1 Early palliative care vs standard oncological care, Outcome 2 Depression.

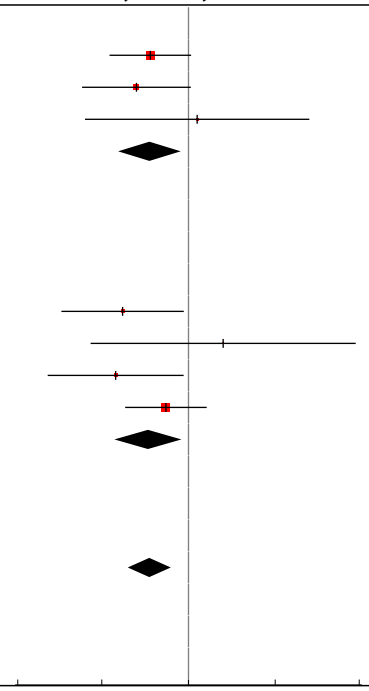
Study or subgroup	Treatment as usual	Early palliative care	Std. Mean Difference	Std. Mean Difference	Weight	Std. Mean Difference
	N	N	(SE)	IV, Random, 95% CI		IV, Random, 95% CI
1.2.1 Co-ordinated care model						
Bakitas 2009	134	145	-0.1 (0.12)		39.21%	-0.15[-0.39,0.09]
Bakitas 2015	83	72	0.1 (0.16)		22.05%	0.06[-0.25,0.37]
McCorkle 2015	56	36	0.1 (0.28)		7.2%	0.11[-0.44,0.66]
Subtotal (95% CI)					**68.46%**	**-0.06[-0.23,0.12]**
Heterogeneity: Tau²=0; Chi²=1.49, df=2(P=0.47); I²=0%						
Test for overall effect: Z=0.61(P=0.54)						
1.2.2 Integrated care model						
Maltoni 2016	65	64	-0.2 (0.18)		17.42%	-0.25[-0.6,0.1]
Temel 2010	47	60	-0.2 (0.2)		14.11%	-0.23[-0.62,0.16]
Subtotal (95% CI)					**31.54%**	**-0.24[-0.5,0.02]**
Heterogeneity: Tau²=0; Chi²=0.01, df=1(P=0.94); I²=0%						
Test for overall effect: Z=1.8(P=0.07)						
Total (95% CI)					**100%**	**-0.11[-0.26,0.03]**
Heterogeneity: Tau²=0; Chi²=2.82, df=4(P=0.59); I²=0%						
Test for overall effect: Z=1.51(P=0.13)						
Test for subgroup differences: Chi²=1.32, df=1 (P=0.25), I²=24.46%						

Analysis 1.3. Comparison 1 Early palliative care vs standard oncological care, Outcome 3 Survival.

Study or subgroup	Treatment as usual	Early palliative care	log[Hazard Ratio]	Hazard Ratio	Weight	Hazard Ratio
	N	N	(SE)	IV, Random, 95% CI		IV, Random, 95% CI
Bakitas 2009	161	161	-0.2 (0.15)		26.82%	0.8[0.6,1.08]
Bakitas 2015	103	104	-0.4 (0.21)		23.68%	0.64[0.42,0.96]
Tattersall 2014	60	60	0.5 (0.19)		24.75%	1.6[1.1,2.32]
Temel 2010	74	77	-0.5 (0.19)		24.75%	0.63[0.44,0.92]
Total (95% CI)					**100%**	**0.85[0.56,1.28]**
Heterogeneity: Tau²=0.14; Chi²=15.55, df=3(P=0); I²=80.71%						
Test for overall effect: Z=0.78(P=0.43)						

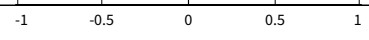
Analysis 1.4. Comparison 1 Early palliative care vs standard oncological care, Outcome 4 Symptom intensity.

Study or subgroup	Early palliative care N	Treatment as usual N	Std. Mean Difference (SE)	Std. Mean Difference IV, Random, 95% CI	Weight	Std. Mean Difference IV, Random, 95% CI
1.4.1 Co-ordinated care model						
Bakitas 2009	145	134	-0.2 (0.12)		27.83%	-0.22[-0.46,0.02]
Bakitas 2015	72	83	-0.3 (0.16)		15.65%	-0.3[-0.61,0.01]
McCorkle 2015	30	28	0.1 (0.33)		3.68%	0.05[-0.6,0.7]
Subtotal (95% CI)					**47.16%**	**-0.23[-0.41,-0.04]**
Heterogeneity: Tau^2=0; Chi^2=0.92, df=2(P=0.63); I^2=0%						
Test for overall effect: Z=2.45(P=0.01)						
1.4.2 Integrated care model						
Maltoni 2016	64	65	-0.4 (0.18)		12.37%	-0.38[-0.73,-0.03]
Tattersall 2014	13	13	0.2 (0.39)		2.63%	0.2[-0.56,0.96]
Temel 2010	60	47	-0.4 (0.2)		10.02%	-0.42[-0.81,-0.03]
Zimmermann 2014	151	149	-0.1 (0.12)		27.83%	-0.13[-0.37,0.11]
Subtotal (95% CI)					**52.84%**	**-0.23[-0.43,-0.04]**
Heterogeneity: Tau^2=0.01; Chi^2=3.51, df=3(P=0.32); I^2=14.43%						
Test for overall effect: Z=2.37(P=0.02)						
Total (95% CI)					**100%**	**-0.23[-0.35,-0.1]**
Heterogeneity: Tau^2=0; Chi^2=4.42, df=6(P=0.62); I^2=0%						
Test for overall effect: Z=3.58(P=0)						
Test for subgroup differences: Chi^2=0, df=1 (P=0.95), I^2=0%						



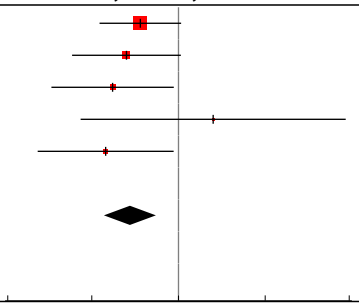
Analysis 1.5. Comparison 1 Early palliative care vs standard oncological care, Outcome 5 Health-related quality of life (sensitivity analysis for study design including RCTs only).

Study or subgroup	EPC N	TAU N	Std. Mean Difference (SE)	Std. Mean Difference IV, Random, 95% CI	Weight	Std. Mean Difference IV, Random, 95% CI
Bakitas 2009	145	134	0.3 (0.12)		40.62%	0.27[0.03,0.51]
Bakitas 2015	72	83	0.2 (0.16)		22.85%	0.19[-0.12,0.5]
Maltoni 2016	64	65	0.3 (0.18)		18.05%	0.33[-0.02,0.68]
Tattersall 2014	13	13	0.1 (0.39)		3.85%	0.06[-0.7,0.82]
Temel 2010	60	47	0.5 (0.2)		14.62%	0.52[0.13,0.91]
Total (95% CI)					**100%**	**0.29[0.14,0.44]**
Heterogeneity: Tau^2=0; Chi^2=2.14, df=4(P=0.71); I^2=0%						
Test for overall effect: Z=3.81(P=0)						



Analysis 1.6. Comparison 1 Early palliative care vs standard oncological care, Outcome 6 Symptom intensity (sensitivity analysis for study design including RCTs only).

Study or subgroup	EPC N	TAU N	Std. Mean Difference (SE)	Std. Mean Difference IV, Random, 95% CI	Weight	Std. Mean Difference IV, Random, 95% CI
Bakitas 2009	145	134	-0.2 (0.12)		40.62%	-0.22[-0.46,0.02]
Bakitas 2015	72	83	-0.3 (0.16)		22.85%	-0.3[-0.61,0.01]
Maltoni 2016	64	65	-0.4 (0.18)		18.05%	-0.38[-0.73,-0.03]
Tattersall 2014	13	13	0.2 (0.39)		3.85%	0.2[-0.56,0.96]
Temel 2010	60	47	-0.4 (0.2)		14.62%	-0.42[-0.81,-0.03]
Total (95% CI)					**100%**	**-0.28[-0.43,-0.13]**
Heterogeneity: Tau^2=0; Chi^2=2.58, df=4(P=0.63); I^2=0%						
Test for overall effect: Z=3.66(P=0)						



APPENDICES

Appendix 1. Search strategy for MEDLINE (OvidSP)

1. exp Palliative Care/

2. palliat*.tw.

3. "advanced disease*".tw.

4. ("end-stage disease*" or "end stage disease* or end-stage illness" or "end stage").tw.

5. Terminally Ill/

6. Terminal Care/

7. (terminal* adj6 care*).tw.

8. ((terminal* adj6 ill*) or terminal-stage* or dying or (close adj6 death)).tw.

9. (terminal* adj6 disease*).tw.

10. (end adj6 life).tw.

11. hospice*.tw.

12. or/1-11

13. exp Neoplasms/

14. (neoplasm* or cancer* or tumo?r*).tw.

15. or/13-14

16. 12 and 15

17. randomized controlled trial.pt.

18. controlled clinical trial.pt.

19. randomized.ab.

20. placebo.ab.

21. clinical trials as topic.sh.

22. randomly.ab.

23. trial.ti.

24. 17 or 18 or 19 or 20 or 21 or 22 or 23

25. exp animals/ not humans.sh.

26. 24 not 25

27. 16 and 26

Appendix 2. Seach strategy for CENTRAL (the Cochrane Library)

#1 MESH DESCRIPTOR Terminal Care EXPLODE ALL TREES

#2 palliat*

#3 ("advanced disease*")

#4 (("end-stage disease*" or "end stage disease* or end-stage illness" or "end stage"))

#5 MESH DESCRIPTOR Terminally Ill

#6 MESH DESCRIPTOR Terminal Care

#7 ((terminal* near/6 care*))

#8 (((terminal* near/6 ill*) or terminal-stage* or dying or (close near/6 death)))

#9 ((terminal* near/6 disease*))

#10 ((end near/6 life))

#11 hospice*

#12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11

#13 MESH DESCRIPTOR Neoplasms EXPLODE ALL TREES

#14 ((neoplasm* or cancer* or tumo?r*))

#15 #13 OR #14

#16 #12 AND #15

Appendix 3. Seach strategy for Embase (OvidSP)

1. exp Palliative Care/

2. palliat*.tw.

3. Terminally Ill/

4. Terminal Care/

5. (terminal* adj6 care*).tw.

6. ((terminal* adj6 ill*) or terminal-stage* or dying or (close adj6 death)).tw.

7. (terminal* adj6 disease*).tw.

8. (end adj6 life).tw.

9. hospice*.tw.

10. ("end-stage disease*" or "end stage disease* or end-stage illness" or "end stage").tw.

11. "advanced disease*".tw.

12. or/1-11

13. exp Neoplasms/

14. (neoplasm* or cancer* or tumo?r*).tw.

15. or/13-14

16. 12 and 15

17. random$.tw.

18. factorial$.tw.

19. crossover$.tw.

20. cross over$.tw.

21. cross-over$.tw.

22. placebo$.tw.

23. (doubl$ adj blind$).tw.

24. (singl$ adj blind$).tw.

25. assign$.tw.

26. allocat$.tw.

27. volunteer$.tw.

28. Crossover Procedure/

29. double-blind procedure.tw.

30. Randomized Controlled Trial/

31. Single Blind Procedure/

32. or/17-31

33. (animal/ or nonhuman/) not human/

34. 32 not 33

35. 16 and 34

36. limit 35 to embase

Appendix 4. Seach strategy for PsycINFO (OvidSP)

1. exp Palliative Care/

2. palliat*.tw.

3. Terminally Ill Patients/

4. (terminal* adj6 care*).tw.

5. ((terminal* adj6 ill*) or terminal-stage* or dying or (close adj6 death)).tw.

6. (terminal* adj6 disease*).tw.

7. (end adj6 life).tw.

8. hospice*.tw.

9. ("end-stage disease*" or "end stage disease* or end-stage illness" or "end stage").tw.

10. "advanced disease*".tw.

11. exp Neoplasms/

12. (neoplasm* or cancer* or tumo?r*).tw.

13. or/11-12

14. or/1-10

15. 13 and 14

16. clinical trials/

17. (randomis* or randomiz*).tw.

18. (random$ adj3 (allocat$ or assign$)).tw.

19. ((clinic$ or control$) adj trial$).tw.

20. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.

21. (crossover$ or "cross over$").tw.

22. random sampling/

23. Experiment Controls/

24. Placebo/

25. placebo$.tw.

26. exp program evaluation/

27. treatment effectiveness evaluation/

28. ((effectiveness or evaluat$) adj3 (stud$ or research$)).tw.

29. or/16-28

30. 15 and 29

Appendix 5. Search strategy for CINAHL (EBSCO)

S6	S1 AND (S2 OR S3) AND S4 AND S5
S5	(cancer OR neoplasm* OR tumor* OR tumour* OR malignan*)
S4	(early AND OR timely OR proactive OR (early AND care) OR (early AND treatment*) OR (early AND medicine* OR (early AND surgery) OR (early AND therapy))
S3	(best AND support*) OR (optim* AND support*) OR (best AND care) OR (best AND treatment*) OR *supportive care*
S2	((palliate* OR (terminal* AND ill*) OR (terminal* AND caring) OR (terminal* AND care*) OR bereave* OR hospice*) OR euthanas* OR (attitude* AND death*) OR (assist* AND death*) OR (assist* AND die*) OR (assist* AND suicide*) OR (help* AND death*) OR (help* AND die*) OR (help* AND suicide*) OR (aid* AND death*) OR (aid* AND die*) OR (aid* AND suicide*) OR (right* AND die*) OR (respite AND care*) OR (respite AND caring) OR (living AND will*) OR (advance* AND directive*) OR (advance* AND care AND plan) OR (“end of life” AND care) OR (“end of life” AND caring))

(Continued)

S1	(randomized controlled Trial* OR controlled clinical trial* OR placebo OR randomly OR Trial*)

Appendix 6. Search strategy for OpenGrey (EXALEAD)

(randomized controlled trial OR controlled clinical trial OR placebo OR randomly OR trial) AND ((palliate* OR (terminal* AND ill*) OR (terminal* AND caring) OR (terminal* AND care*) OR bereave* OR hospice*) OR euthanas* OR (attitude* AND death*) OR (assist* AND death*) OR (assist* AND die*) OR (assist* AND suicide*) OR (help* AND death*) OR (help* AND die*) OR (help* AND suicide*) OR (aid* AND death*) OR (aid* AND die*) OR (aid* AND suicide*) OR (right* AND die*) OR (respite AND care*) OR (respite AND caring) OR (living AND will*) OR (advance* AND directive*) OR (advance* AND care AND plan) OR (“end of life” AND care) OR (“end of life” AND caring) OR ((chemoth* AND (induced AND vomiting)) OR (chemoth* AND (induced AND sickness))) OR (chemoth* AND (related AND sickness)) OR (chemoth* AND (related AND vomiting))) OR ((induced AND hypersalivation) OR (induced AND hyposalivation)) OR (induced AND xerostomi*) OR ((induced AND cachexi*) OR (related AND cachexi*)) OR ("terminal* ill*"AND "symptom* management"))) OR (((anorexi* AND cancer*) OR (anorexi* AND carcinoma*)) OR ((anorexi* AND radiotherap*)))) OR Search (((cancer AND weight-loss) OR (cancer AND weight AND loss) OR (cancer AND weight AND losing) OR (carcinoma* AND weight-loss) OR (carcinoma* AND weight AND loss) OR (carcinoma* AND weight AND losing))) OR ((((cancer AND weight-gain*) OR (cancer AND weight AND gain*) OR (carcinoma* AND weight-gain) OR (carcinoma* AND weight AND gain*)))) OR (((cancer AND appetite AND stimulat*) OR (carcinoma* AND appetite AND stimulat*))) OR (((appetite AND stimulat*) OR ((cancer AND hot AND flush*) OR (cancer AND hot AND flash*)) OR (related AND cachexi*) OR (neoplastic AND cachexi*) OR ((induced AND constipat*) OR (induced AND emesis)) OR (opioid AND induced) OR (morphine AND induced) OR (methadone AND induced) OR (cancer or carcinoma* AND music AND therapy) OR ((cancer or carcinoma*) AND ((aroma AND therapy) OR aromatherapy))) OR ((dysphag* AND cancer) OR ((symptom AND control AND (cancer OR carcinoma*)) OR (radiotherap* AND induced) OR (chemotherap* AND induced) OR (radiotherap* AND related) OR (chemotherap* AND related) OR ((cancer AND related) OR (carcinoma* AND related)) OR (anorexi* AND radiochemotherap*))) AND ((best AND support*) OR (optim* AND support*) OR (best AND care) OR (best AND treatment*) OR “supportive care”)((best AND support*) OR (optim* AND support*) OR (best AND care) OR (best AND treatment*) OR “supportive care”) AND (early AND OR timely OR proactive OR (early AND care) OR (early AND treatment*) OR (early AND medicine* OR (early AND surgery) OR (early AND therapy)) AND (cancer OR neoplasm* OR tumor* OR tumour* OR malignan*)

CONTRIBUTIONS OF AUTHORS

MWH drafted the protocol, developed and ran the search strategy, obtained copies of studies, selected studies for inclusion, extracted data from studies, entered data into RevMan, carried out and interpreted the analysis, and drafted the review. SE ran the search strategy, obtained copies of studies, selected studies for inclusion, extracted data from studies, and entered data into RevMan. GR drafted the protocol and assisted in carrying out and interpreting the analyses, and in drafting the final review. HCF and MT drafted the protocol, interpreted the analyses, and drafted the final review. MV interpreted the analyses from a clinical point of view and drafted the final review. MH drafted the protocol, developed the search strategy, selected studies for inclusion (as arbiter), supervised in carrying out and interpreting the analyses, and drafted the review.

DECLARATIONS OF INTEREST

MWH: none known; MWH is an internal medicine physician (internist) and a junior research group leader in mental health services research.

SE: none known.

GR: none known.

HCF: none known; HCF is a specialist in psychosomatic medicine and internal medicine, and manages psychiatric comorbidity in patients with somatic illnesses.

MV: none known; MV is a specialist oncology and palliative care physician and manages patients with advanced cancer.

MT is a department head of thoracic oncology (Thoraxklinik, University of Heidelberg) and manages patients with malignant thoracic diseases and lung metastases. MT received personal consulting fees from Lilly, Novartis, Roche, AstraZeneca, Pfizer, Boehringer, and BMS in 2014; from Lilly, Novartis, Roche, AstraZeneca, BMS, MSD, Pfizer, Boehringer, and Celgene in 2015; and from Lilly, Novartis, Roche, AstraZeneca, BMS, MSD, Pfizer, Boehringer, and Celgene in 2016 for attending boards. MT received lecture fees from Lilly, Novartis, Roche, AstraZeneca, Pfizer, and Boehringer in 2014; from Lilly, Novartis, Roche, AstraZeneca, BMS, MSD, Pfizer, and Boehringer in 2015; and from Lilly, Novartis, AstraZeneca, BMS, MSD, Pfizer, Boehringer, and Celgene in 2016.

MH: none known.

SOURCES OF SUPPORT

Internal sources

- Heidelberg University Hospital, Germany.

  Employer of MWH, SE, MV, MT, and MH
- University Medical Center Freiburg, Germany.

  Employer of GR
- University of Duesseldorf, Germany.

  Employer of HCF

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We updated and added references to the Background and Methods sections. In the Background section, we updated our definition of 'early palliative care' on the basis of current literature and introduced the recently conceptualised classification of models for early palliative care provided by Hui 2015a. In the Methods section, we documented our decision to conduct a subgroup analysis for two different models. In the 'Types of interventions' section, we specified as an additional inclusion criterion 'An early palliative care intent had to be stated explicitly or be reflected in the sample composition, i.e. most participants had to be enrolled shortly after diagnosis of advanced disease.' In the 'Assessment of risk of bias in included studies' section, we now state that we included blinding of participants and outcome assessment as sixth and seventh domains in the risk of bias assessment. Also in this section, we updated our justification for not excluding small studies from the review. We refrained from compiling funnel plots because of the small number of included studies. In light of new recommendations by the GRADE Working Group (Alonso-Coello 2016), we have replaced the term "quality of the evidence", which we had used in the protocol, with the term "certainty of the evidence". For reasons of completeness, we reported results on outcomes in the review that had not been prespecified in the protocol (i.e. place of death, problems with medical interactions and satisfaction with care, and illness and prognosis understanding). Furthermore, we now explicitly state that we based survival analysis on unadjusted death hazard ratios. To enhance comprehensibility, we decided to refrain from additionally converting SMDs to odds ratios. We have explained in the Methods section all post-protocol decisions concerning methods.

INDEX TERMS

Medical Subject Headings (MeSH)

*Palliative Care; *Quality of Life; Communication; Neoplasms [pathology] [*psychology] [*therapy]; Physician-Patient Relations

MeSH check words

Humans