The impact of Specialized Palliative Care on cancer patients' Health-Related Quality of Life: A systematic review and meta-analysis

Angelos P. Kassianos[1*] (0000-0001-6428-2623), Myria Ioannou[2], Marianna Koutsantoni[2], Haris Charalambous[3]

[1] University College London, Department of Applied Health Research, London, UK

[2] University of Cyprus, Department of Psychology, Nicosia, Cyprus

[3] Bank of Cyprus Oncology Centre, Nicosia, Cyprus

*** Corresponding author:** UCL, Department of Applied Health Research, 1-19 Torrington Place, London, WC1E 7HB, UK angelos.kassianos@ucl.ac.uk

Abstract (250 words)

Purpose

Specialized Palliative Care (SPC) is currently underutilized or provided late in cancer care. The aim of this systematic review and meta-analysis is to critically evaluate the impact of SPC on patients' Health-Related Quality of Life (HRQoL).

Methods

Five databases were searched through June 2016. Randomized Controlled Trials (RCTs) and prospective studies using a pre- and post- assessment of HRQoL were included. The PRISMA reporting statement was followed. Criteria from available checklists were used to evaluate the studies' quality. A meta-analysis followed using random-effect models separately for RCTs and non-RCTs.

Results

Eleven studies including five RCTs and including 2939 cancer patients published between 2001 and 2014 were identified. There was improved HRQoL in patients with cancer following SPC especially in symptoms like pain, nausea and fatigue as well as improvement of physical and psychological functioning. Less or no improvements were observed in social and spiritual domains. In general, studies of inpatients showed a larger benefit from SPC than studies of outpatients whereas patients' age and treatment duration did not moderate the impact of SPC. Methodological shortcomings include high attrition rates, low precision and power and poor reporting of control procedures.

Conclusions

The methodological problems and publication bias call for higher-quality studies to be designed, funded and published. However, there is a clear message that SPC is multi-disciplinary and aims at palliation of symptoms and burden in line with current recommendations.

Keywords: palliative care, specialized palliative care, cancer, quality of life, meta-analysis

Introduction

Cancer is a public health and epidemiological concern with estimated 14 million new cases per year worldwide, two thirds of which are expected to die within one year [1]. A recent statement from the American Society of Clinical Oncology (ASCO) came to recognize that patients with advanced incurable cancer face complex physical, psychological, social, and spiritual consequences of disease and its treatment [2]. Moreover, the care for these patients should include an individualized assessment of each patient's needs, goals, and preferences throughout the course of the illness [3]. For these patients, oncological treatment at late stages of disease has limited benefits in terms of prolonging life [4–7]. Furthermore the ASCO statement recognizes that standard oncology care for these patients remains focused on disease-directed therapy, often without realistic conversations about its potential benefits and limitations and the potential role of Palliative Care (PC). [2]. This results in increased aggressiveness of care and subsequently in increased toxicity and worsening of physical symptoms, whilst neglecting to address the physical, psychological and spiritual impact of the disease and its treatment [8], with emerging evidence that aggressive care can actually decrease patients' Health-Related Quality of Life (HRQoL) before death [9].

Consequently, PC comes to address this challenge for patients with advanced cancer. The World Health Organization (WHO) defines PC as provision of active, holistic care of patient with advanced, progressive illness focusing on the management of pain and other symptoms and provision of psychological, social and spiritual support with the aim to improve HRQoL [10]. HRQoL is a multidimensional concept, which interprets an individual's health status. Any increase in disease-related symptoms is

also related to a decrease of HRQoL [11]. To achieve improvement in HRQoL, PC aims to control for the burden of symptoms, provide psycho-social support, co-ordinate care for patients and families and provide hospice services [12–14].

Specialized PC (SPC) underscores the specialist training in PC that specialist clinicians undergo, and the certification that currently exists for PC as a new medical specialty, whilst generalist or basic PC refers to the basic symptom control and care provided by non PC specialists, e.g. general physicians or oncologists [15].

SPC provision has been very rapidly growing the last decade in the US [16] and associated with improvements in HRQoL in a non-cancer specific review [17]. However, methodological shortcomings of research studies evaluating SPC delivery are evident from non-disease specific SPC studies including contamination of control groups as well as limitations in recruitment, attrition and adherence which compromise the robustness of the impact of SPC [18]. High attrition rates and heterogeneity of study population and description of procedures in both the intervention and control arms are other issues from similar studies [19]. These methodological issues are reflected in limitations of evaluation of health care services where heterogeneity is identified in terms of interventions and methods [20].

There are recommendations suggesting that SPC should be integrated to oncological treatment to improve patients' HRQoL [18, 21–24]. In fact, ASCO recommends offering SPC with oncological treatment for all patients treated for metastatic cancer or with uncontrolled symptoms [25, 26]. However, more evidence is needed on how to implement these recommendations [18]. Thus, there is a need to have more concrete, solid evidence of the impact of SPC in HRQOL for policy making since it is generally accepted that HRQoL is the most significant endpoint in SPC studies. The

aim of this systematic review and meta-analysis is to evaluate the impact of SPC on cancer patients' HRQoL.

Methods

The protocol for the systematic review was registered with the PROSPERO international prospective register of systematic reviews (Registration number: CRD420150161121) in January 2015. The PRISMA statement reporting items for systematic reviews and meta analyses was followed [27]. The main assessed outcome was HRQoL.

Eligibility criteria

Studies published in peer-reviewed journals were eligible to be reviewed, provided that they included patients > 18 years old, diagnosed with any primary and metastatic cancer. Eligible studies should be evaluating interventions aiming to provide SPC to cancer patients by SPC service and assessing HRQoL as an outcome. For PC, the WHO definition was used to assess eligibility [10]. The WHO definition was used as it clearly describes palliative care. This was the first step in identifying whether PC was used. The second was to assess whether SPC was delivered as care provided from professionals/teams with training/expertise in PC, who coordinate or provide comprehensive care for cancer patients [18, 28]. Studies that provided supportive care or any other psychosocial intervention or care that was not coordinated or provided by SPC team were excluded. Studies that included cancer patients together with other patient groups or where HRQoL was not assessed using standardized and validated questionnaires were also excluded. Both randomized and non-randomized controlled trials including prospective and retrospective studies with pre- and post- assessment were included. Cross-sectional and qualitative studies as well as pilot studies were

excluded. No publication date restriction was used and only studies published in English were included for pragmatic reasons.

Search strategy, study selection, and synthesis

The initial search was conducted between January and March 2015 and updated in June 2016. The search keywords were developed around three conceptual areas: the type of care, the type of patients, and the measured outcome. The following search strategy was applied for all the databases: ('palliative * car*' OR 'comfort* car*' OR 'end?of?life car*' OR 'terminal car*' OR 'support* car*' OR 'hospice') AND ('cancer patient*' OR 'advance cancer patient*' OR 'patient*') AND ('quality of life' OR 'health?related quality'). The search was in line with the PRESS checklist [29]. The search strategy applied for all the databases is available as Electronic Supplementary Material. A pilot-testing scoping search identified 5440 studies.

The following databases were searched: EMBASE, CINAHL, MEDLINE, PsycINFO, and PubMed. Two authors (MI, MK) who imputed all the identified titles in a database conducted the searches independently. After removing duplicates, the titles were screened based on the eligibility criteria and inclusion of at least two keywords in the title. Three authors (AK, MI, MK) then screened abstracts independently. Eligible studies based on abstract were included in full text screening and data extraction. After abstract screening, hand searches of included studies' reference lists followed.

During the full-text screening, an assessment form was used to extract the data from the identified studies. Three authors (AK, MI, MK) extracted data independently with crosschecking between them. Discrepancies were discussed and resolved aiming to reach mutual agreement. The final studies were provided to a fourth author (HC) with

clinical experience to provide clinical evaluation (Figure 1) to ensure that the intervention described was SPC (i.e. provided by teams with specialist training in PC). The evidence from the included studies was synthesized using a narrative analysis approach.

Quality appraisal

Three authors (AK, MI, HC) conducted a quality assessment of included studies. The consistency among the quality ratings was assessed using the inter-rater reliability (IRR) kappa. Discrepancies were discussed and resolved in consensus meetings. The quality criteria were adapted from relevant quality checklists [30–38]. The main areas assessed were on the procedures of the randomization, the intervention, the appropriate description of the patient-related aspects, and the internal and external validity of the study. All studies were scored (0-2) on each quality criterion, and a summative score was calculated for each study. Highest score possible for RCTs was 32 and for non-RCTs 22. Scores were interpreted in terms of percentage (i.e. obtaining 13/26 points = 50%). The Quality Assessment Criteria List is available as Electronic Supplementary Material.

Meta-Analysis

None of the studies had a score that significantly differed from the mean of the summative score derived from the quality assessment. Therefore all studies were included in the meta-analysis. The meta-analysis was run based on the principles of the random-effects models, which recognize the differences in error variation between the studies. The standardized mean difference (SMD) was used, as it takes into account that HRQoL was measured using different tools and calculated using the equation:

$$SMD = \frac{Difference\ in\ mean\ outcome\ between\ groups}{SD\ of\ outcome\ among\ patients}$$

The fixed-effects model was run first to estimate the heterogeneity between the studies (Q and I_2 statistic) and then the random-effects models if heterogeneity was significant. Moreover, sensitivity analyses were run to show the robustness of the findings based on the decisions made earlier regarding the inclusion criteria. When a study used a score to assess overall quality of life, this was used as an outcome whereas in the studies where this variable was not used, a summative score of quality of life based on measured outcomes was used. For sub-group analyses, mixed effects models were used to assess the potential predictive value of certain factors for the estimation of the effect size (Cohen's d). The Q statistic was used to determine if a factor significantly differentiates the effect size between the groups. Similarly, to investigate the predictive role of age and treatment duration a meta-regression model was used. When the effect size estimates were not reported, they were computed through the available formulas or were transformed to the effect size indexes used in the current meta-analysis. The factors used in the models were trial design (RCTs and non-RCTs), type of cancer, site of treatment (inpatients, outpatients, and both), SPC duration, and patients' age. Publication bias was also investigated to detect asymmetries between studies.

Results

Study selection

The initial search identified 8649 records from five databases and following all screening stages eleven studies were included in the systematic review (Figure 1).

Exclusions were mainly based on type of treatment, language, study population and research design with the majority not reporting any intervention or SPC.

Study characteristics

Eleven studies (N = 11) were included in the review with a total of 2939 patients with gastrointestinal tract, lung, breast, female genitals, prostate, male genitals, kidney, vesical, urethra, lymphoma, skin/melanoma, sarcoma, colorectal, head and neck, pancreatic, stomach, liver, bladder, esophageal, bile duct, and ovarian cancer. Three studies were conducted in the USA, two in Canada and one each in Japan, Norway, Sweden, Switzerland, Denmark and Turkey published between 2001 and 2014. Data were collected between 1995 and 2011. Five were RCTs (Table 1) and six were prospective studies that assessed HRQoL in a cohort of patients before and after implementing SPC (Table 2). Of the five RCTs, two were clustered. Two RCTs reported using participant blinding and in a third one the patients in the intervention arm were not aware of the other arm. All RCTs used a stratified approach in randomization.

The mean age of the patients ranged from 52.6 to 68 years with one study reporting a median of 72. Four studies (36.4%) used inpatients; three (27.2%) used outpatients; four studies (36.4%) used both. For example, SPC was delivered in a PC unit or clinic [11, 39–41], at home [42, 43], at community services [44] or used a combination of home-based care and clinical appointments [45–47]. Seven studies (58.3%) specified that they included patients with metastatic cancer, whilst four studies reported stage of cancer as stage III or IV. Three studies specified that the referral to SPC was within 8 weeks [42, 45] or up to twelve weeks after diagnosis [47]. Only three studies (27.2%) provided prognosis information for included patients at study entry and it ranged from six to twenty-four months.

There was variation of tools used to measure HRQoL; the EORTC QLQ C-30 [48], the Functional Assessment of Cancer Therapy (FACT) measurement system [49, 50], the Functional Assessment of Chronic Illness Therapy-Palliative Care (FACIT-pal) [51, 52] and its lung subscale (FACT-L) [53], the spiritual subscale (FACIT-sp) [54], the QUAL-E [55], the McGill QoL Questionnaire [56], the Schedule for the Evaluation of Individual Quality of Life – Direct Weighting version (SEIQoL-DW) [57], and the Assessment of Quality of Life at the End of Life (AQEL) [58].

Intervention and control procedures

The SPC was clearly outlined in two studies [45, 47] while another two studies [11, 59] failed to clearly report details on SPC delivery but described SPC provided by a multi-professional team with specialist training in PC. A fourth study also did not report on the intervention but referred to a methodological paper [44]. A fifth study had no information on what the SPC entailed other than who delivered care [41].

Almost half of the studies reported the theoretical background or guidelines of the SPC used. For example, one study [47] reported using the chronic care model focusing on case management in relation to communication with family and clinicians in terms of life priorities, goals and preferences. Case management SPC was also used in another study [39] whilst two studies [42, 45] reported using an approach focusing on symptom assessment, decision-making, care co-ordination and patients' goals and needs.

All studies reported on the team or health professionals delivering the SPC except one which was an inpatient study that usually incorporates a multidisciplinary team of professionals [59]. Six studies (54.5%) reported a multi-disciplinary team delivering the intervention. All of the teams included PC-trained nurses and clinicians and some

of them included psychologists, social workers and other specialized professionals. Only five studies (45.5%) reported providing training to the team delivering the intervention [39, 42, 44–46].

The control groups' procedures were reported in four RCTs as 'usual care' [39, 42, 45, 47], while the fifth RCT reported no information [46]. The SPC group procedures ranged from daily to monthly sessions and from one-to-two weeks to four months (Table 3).

Study outcomes

We report the outcomes of the five RCT's first. In terms of the baseline assessment, two [42, 47] reported no differences in HRQoL between the intervention and control arms at baseline and one [39] provided only baseline differences on symptoms as measured by the Edmonton Symptom Assessment System (ESAS). The outcome measures were worse at baseline in the intervention group with one study reporting more genitourinary cancer cases in the intervention group [45]. Another study reported differences in housing, access to informal help, home care nursing and living situation [46].

In terms of the primary endpoint, all of the RCTs with the exception of one study [46], showed some evidence of improvement of HRQoL in the intervention compared to the control arm (Table 1). The study that did not, investigated the impact of a newly founded PC unit, which was set up in 1994, providing SPC in collaboration with existing community services in Norway, with the study being carried out between 1995-1997. Neither the PMU staff nor the community workers had any experience with the overall concept and the new routines that were to be

implemented. Also, the intervention was strongly based on the existing community service.

The study by Bakitas et al followed findings with intention-to-treat analyses which confirmed the positive impact of SPC on HRQoL [47]. Another study of inpatient SPC by Oczelik et al, reported improvements on role, emotional and social functioning and on the global quality of life item [39]. Sustained benefits were reported in the study by Zimmermann et al, four months post-intervention, but not at the pre-specified time of analysis of the primary outcome which was change in the FACIT-Sp score at 3 months [45]. Finally the study by Temel et al, reported clinically meaningful improvements on HRQoL [42].

All non-randomized studies showed significant improvements in HRQoL following the SPC intervention (Table 2). The study by Bishoff et al, showed significant improvement in the general quality of life items, and also in symptoms like pain and fatigue between baseline and first and second follow-ups, with sustained benefits twelve weeks post-intervention [40]. Similarly Cohen et al reported improvements in physical functioning as well as in physical and psychological domains during the first week of admission to a SPC unit [59]. The study by Melin-Johanson et al [43] found that social and existential domains did not improve.

Looking at both RCTs and non-randomized studies together, there were some other important findings, which are useful at interpreting the impact of SPC on HRQoL. SPC delivery led to lower symptom intensity overall [39, 47] and specifically on pain [11, 40, 59], fatigue, [40] and nausea [43]. There were also improvements in symptoms of depression [40, 59], mood [42], anxiety [40, 43, 59] and spiritual well being [40, 59]. Patients who received SPC were more likely to die at home [44, 46]

and be more satisfied with care [39, 45]. There were two studies also reporting a positive impact on survival [42, 47].

Physical functioning was not improved by SPC in the Jordhoy et al and Ozcelik et al trials [39, 46]. Additionally in the Jordhoy et al trial emotional functioning and pain and in Ozcelik et al cognitive functioning did not improve. Finally, in the Melin-Johansson et al trial [43] the social and existential functioning of patients remained the same.

Quality assessment

The inter-rater reliability on quality assessment was high (kappa = 0.82). The summative quality scores ranged from 36.4% to 78.1% demonstrating that studies achieved the methodological standards on a moderate degree with an average of 56.8% quality score (Table 4). The quality of RCTs was higher than non-RCTs because of better reporting and consideration of research design methods with average summative quality scores of 65.0% and 50.0% respectively. Most studies had well defined objectives and hypotheses.

Six studies were either underpowered or failed to report any power calculation [11, 40, 43, 44, 46, 59]. The precision of the included studies was also problematic since the Confidence Intervals (CIs) around the estimated treatment effect size were either wide with high possibilities of random error [11, 44, 46, 59], or rather wide with moderate possibilities for random error for the rest of the studies. In terms of reporting, two studies [39, 46] did not report the number of eligible patients.

Attrition rates for each study were calculated using the reported numbers of participants at baseline and at the end of the study as well as the reasons for attrition (Figure 2). The average attrition rates were between 29.1% - 46.6% with three

outliers, two of them with reported attrition of 0% [39, 43] and a third study with reported attrition of 75.1% [46]. Using information in five studies [11, 42, 45, 47, 59] there were 190 deaths and 210 withdrawals and for two studies reasons for attrition were not reported [40, 59]. For another study [41], the third week post- intervention was used to calculate attrition since the HRQoL data reported are from that point.

Meta-analysis

The included RCTs were homogeneous to be analyzed with fixed-effects models (Q= 8.22, p= .084, I_2= 51.32 %) but there was heterogeneity in non-RCTs (Q= 34.889, p< .001, I_2= 85.67%). There was a positive moderate impact of SPC in HRQoL (SMD, 0.28; 95% CI, 0.16 to 0.41; p< .001) (Figure 3). There was also a marginally significant publication bias (Kendall's tau = 0.673, p = .004) favouring studies with positive effect sizes[1].

There were non-significant differences on the impact of SPC on HRQoL between RCTs and non-RCTs (p = .990), types of cancer (p = .627) and between inpatients, outpatients and both (p = .172). However mixed-effects analysis showed that SPC had a positive impact in studies using inpatients (SMD, 0.55; 95% CI, 0.17 to 0.92; p = .004) or both (SMD, 0.18; 95% CI, 0.08 to 0.27; p < .001) but non-significant effect for outpatients (SMD, 0.20; 95% CI, -0.03 to 0.44; p = 0.89).

The meta-regression analyses showed that the patients' age (b = -0.016, 95% CI = -0.038 - 0.007, z = -1.37, p = .17) and treatment duration (b = -0.044, CI = -0.094 - 0.006, z = -1.71, p = .087) were not significant predictors of the overall effect size on HRQoL. The residual error sum of squares was not significant (Q (4) = 8.97, p = .06),

[1] The Duval and Tweedie's trim and fill statistic showed that six studies were missing from the published literature that could establish symmetry on the funnel plot, which even if considered not favoring SPC, the standardized mean effect would remain significant and would still not traverse the zero axis, with d= 0.117 (95% CI -0.012, 0.245).

suggesting that the specialist delivering the intervention largely explained heterogeneity (I_2 = 55.40%).

Discussion

This review suggests that SPC decreases suffering and improves HRQoL in patients with advanced/metastatic cancer. There is evidence of improvement in palliation of symptoms, like pain, nausea, fatigue and improvement of physical and psychological functioning and to a lesser degree social and spiritual. Furthermore in two RCTs, there is evidence of improvement in survival [42, 47]. The meta-analysis also highlights a more pronounced impact of the SPC intervention in studies including inpatients (or both inpatients and outpatients). This may relate to the fact that inpatients are more symptomatic and more in need of SPC. Also, patients' age and treatment duration did not moderate the impact of SPC on HRQoL. On the other hand, studies using a PC team had higher impact on HRQoL compared to case management teams.

This review suggests that the SPC care model in all studies was mostly multi-disciplinary, and aimed at the multi-dimensional nature of suffering. In conducting this review, careful consideration was given to the definition and criteria used to define SPC. In the literature, SPC members have training in PC and either work with or are able to refer to the other members of a multidisciplinary team [60]. In practical terms, in the papers we looked for wordings describing that the personnel delivering care included specialist PC doctors or nurses, hence studies provided by psychologists or other health care professionals without PC training and without the ability to work with established PC teams, were excluded.

In interpreting the meta-analysis the marginally significant publication bias for RCTs needs to be considered. Therefore, journals are advised to publish high quality SPC studies based not only on novelty but also on robust methodology and also to publish protocols or the trials' full data sets. Researchers, ethics committees and funders are also advised to consider these actions [61].

These evidence can support current recommendations, which recognize the importance of SPC in improving patients' symptoms, HRQoL and satisfaction, and suggesting that SPC should be considered early in the course of illness of all patients with advanced/metastatic cancer [25, 26].

There are a number of methodological issues in reported studies including high attrition rates, low precision, low power and poor of the intervention and control procedures. Attrition is a serious limitation with high attrition rates of 40% also identified in non-cancer specific SPC trials [18]. Only three studies used multiple sites calling for more multi-institutional studies to ensure translation of evidence in different health care settings. Furthermore, there has been a multitude of tools used for assessment of HRQoL, with one study using a single-item question [40]. Another important limitation is that in the included RCTs, there is no available information as to the quality of the standard care offered to patients. This lack of standardization can impact the robustness of recommendations and reflects a recent systematic review which showed that only one third of the Best Supportive Care studies offered a detailed description of control procedures [62].

The included studies reflect the findings from a recent review which suggest that strong benefits come from integrated care models involving a multidisciplinary team [63]. Moreover, the included studies varied from predominantly phone-based educational interventions using a SPC nurse and on-going patient and caregiver

follow up [47], outpatient SPC-team approach focusing on illness understanding and management [42], case management [39], home-visit approach for symptom control and support [43] and nurse-led symptom control [11] among others. Another issue identified in terms of delivery is the optimal training in PC of staff and the necessary skill mix in a service providing SPC. Almost half of the included studies did not report training to the team delivering the intervention to ensure systematic implementation. Standardization in methodology should reflect the efforts to standardize SPC through the development of PC programs worldwide, board certification programs in the US and SPC programs in Europe, Canada and Australia [64, 65]. Systematic evaluation is important because there are studies suggesting differences in the proficiency of oncologists to manage pain [66] or on comfort to provide basic PC [18].

Given the fact that current oncological treatment is usually expensive and intensive [67], and the fact that for example in the US, high healthcare costs are not translated into higher quality of care [68], the implementation of SPC should become a public health planning priority [69]. In more than half of the U.S National Cancer Institute's Centres there are SPC services [70] which also increase mostly for inpatients or patients at home [71–73]. Even so, SPC is underutilized [74] so evaluating the implementation of SPC is important.

Limitations of this review include the fact that the reviewed studies come predominantly from countries with advanced health care systems and available PC services. There are no studies from developing countries, where the availability of PC is a much bigger problem [75]. Also the included study criteria were strict to ensure that relevant studies were selected but this led to a small number of studies.

There is a need for further clinical trials to include HRQoL as an end-point together with other parameters including survival, symptom burden, satisfaction with care, caregivers' HRQoL and health care system resources use and costs. This can further facilitate the delivery and quality of services to patients. It is also important that such studies are also undertaken in less developed countries.

Conclusions

The strength of the impact of SPC on HRQoL is particularly reflected in evidence on the sustainability of benefits [40, 45]. This review and future studies can help to shape health care policy in this field and to call for higher quality SPC trials published. The implementation of careful evaluation should persuade policy makers to invest in SPC services.

Conflict of interest

The authors declare no conflict of interest. The authors state that they have full control of all primary data and agree to allow the journal to review them if requested.

References

1. Stewart B, Wild C (2014) IARC Publications Website - World Cancer Report 2014.
2. Peppercorn JM, Smith TJ, Helft PR, et al (2011) American Society of Clinical Oncology Statement: Toward Individualized Care for Patients With Advanced Cancer. J Clin Oncol 29:755–760. doi: 10.1200/JCO.2010.33.1744
3. Care P (1999) Discussing palliative care with patients. Ann Intern Med 130:744–749.
4. Saito AM, Landrum MB, Neville BA, et al (2011) The effect on survival of continuing chemotherapy to near death. BMC Palliat Care 10:14.
5. Von Gruenigen V, Daly B, Gibbons H, et al (2008) Indicators of survival duration in ovarian cancer and implications for aggressiveness of care. Cancer 112:2221–2227.

6. Kao S, Shafiq J, Vardy J, Adams D (2009) Use of chemotherapy at end of life in oncology patients. Ann Oncol 20:1555–1559.

7. Rose JH, O'Toole EE, Dawson NV, et al (2004) Perspectives, preferences, care practices, and outcomes among older and middle-aged patients with late-stage cancer. J Clin Oncol 22:4907–4917.

8. Charalambous H, Silbermann M (2012) Clinically based palliative care training is needed urgently for all oncologists. J Clin Oncol 30:4042–4043.

9. Wright AA, Zhang B, Ray A, et al (2008) Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. Jama 300:1665–1673.

10. World Health Organization (2003) Palliative care: what is it. In: WHO. http://www.who.int/cancer/palliative/definition/en/.

11. Echteld MA, van Zuylen L, Bannink M, et al (2007) Changes in and correlates of individual quality of life in advanced cancer patients admitted to an academic unit for palliative care. Palliat Med 21:199–205.

12. Higginson IJ, Finlay IG, Goodwin DM, et al (2003) Is there evidence that palliative care teams alter end-of-life experiences of patients and their caregivers? J Pain Symptom Manage 25:150–168.

13. Levy MH, Back A, Benedetti C, et al (2009) Palliative Care. J Natl Compr Canc Netw 7:436–473.

14. Ferris FD, Bruera E, Cherny N, et al (2009) Palliative cancer care a decade later: accomplishments, the need, next steps—from the American Society of Clinical Oncology. J Clin Oncol 27:3052–3058.

15. Quill TE, Abernethy AP (2013) Generalist plus specialist palliative care—creating a more sustainable model. N Engl J Med 368:1173–1175.

16. Strand JJ, Mansel JK, Swetz KM, others (2014) The growth of palliative care. Minn Med 97:39–43.

17. Kavalieratos D, Corbelli J, Zhang D, et al (2016) Association between palliative care and patient and caregiver outcomes: a systematic review and meta-analysis. JAMA 316:2104–2114.

18. Zimmermann C, Riechelmann R, Krzyzanowska M, et al (2008) Effectiveness of specialized palliative care: a systematic review. Jama 299:1698–1709.

19. Davis MP, Temel JS, Balboni T, Glare P (2015) A review of the trials which examine early integration of outpatient and home palliative care for patients with serious illnesses. Ann Palliat Med 4:99–121.

20. Jenicek M (1989) Meta-analysis in Medicine where we are and where we want to go. J Clin Epidemiol 42:35–44.

21. Byock I, Twohig JS, Merriman M, Collins K (2006) Promoting excellence in end-of-life care: a report on innovative models of palliative care. J Palliat Med 9:137–151.

22. Morrison RS, Meier DE (2004) Palliative Care. N Engl J Med 350:2582–2590. doi: 10.1056/NEJMcp035232

23. Field MJ, Cassel CK, others (1997) Approaching Death:: Improving Care at the End of Life. National Academies Press

24. Foley KM, Gelband H (2001) Improving palliative care for cancer. Institute of Medicine, National Cancer Policy Board

25. Smith TJ, Temin S, Alesi ER, et al (2012) American Society of Clinical Oncology provisional clinical opinion: the integration of palliative care into standard oncology care. J Clin Oncol 30:880–887.

26. Ferrell BR, Temel JS, Temin S, et al (2016) Integration of Palliative Care Into Standard Oncology Care: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 35:96–112. doi: 10.1200/JCO.2016.70.1474

27. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 151:264–269.

28. WHO | Palliative Care. In: WHO. http://www.who.int/mediacentre/factsheets/fs402/en/. Accessed 24 Jul 2017

29. McGowan J, Sampson M, Lefebvre C (2010) An Evidence Based Checklist for the Peer Review of Electronic Search Strategies (PRESS EBC). Evid Based Libr Inf Pract 5:149–154.

30. Slim K, Nini E, Forestier D, et al (2003) Methodological index for non-randomized studies (MINORS): development and validation of a new instrument. ANZ J Surg 73:712–716.

31. Chalmers TC, Smith H, Blackburn B, et al (1981) A method for assessing the quality of a randomized control trial. Control Clin Trials 2:31–49.

32. Healthcare Improvement Scotland Sign50: A guideline developer's handbbok. http://www.sign.ac.uk/pdf/sign50nov2011.pdf. Accessed 3 May 2016

33. Von Elm E, Altman DG, Egger M, et al (2007) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Prev Med 45:247–251.

34. Jadad AR, Moore RA, Carroll D, et al (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17:1–12.

35. Mowatt G, Grimshaw JM, Davis DA, Mazmanian PE (2001) Getting evidence into practice: The work of the cochrane effective practice and organization of care group (EPOC). J Contin Educ Health Prof 21:55–60. doi: 10.1002/chp.1340210109

36. Des Jarlais DC, Lyles C, Crepaz N (2004) Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: the TREND statement. Am J Public Health 94:361–366.

37. Shea BJ, Grimshaw JM, Wells GA, et al (2007) Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol 7:1.

38. Consort - Welcome to the CONSORT Website. http://www.consort-statement.org/. Accessed 3 May 2016

39. Ozcelik H, Fadiloglu C, Karabulut B, Uyar M (2014) Examining the effect of the case management model on patient results in the palliative care of patients with cancer. Am J Hosp Palliat Med 31:655–664.

40. Bischoff K, Weinberg V, Rabow MW (2013) Palliative and oncologic co-management: symptom management for outpatients with cancer. Support Care Cancer 21:3031–3037.

41. Strömgren AS, Sjogren P, Goldschmidt D, et al (2005) A longitudinal study of palliative care. Cancer 103:1747–1755.

42. Temel JS, Greer JA, Muzikansky A, et al (2010) Early palliative care for patients with metastatic non–small-cell lung cancer. N Engl J Med 363:733–742.

43. Melin-Johansson C, Axelsson B, Gaston-Johansson F, Danielson E (2010) Significant improvement in quality of life of patients with incurable cancer after designation to a palliative homecare team. Eur J Cancer Care (Engl) 19:243–250.

44. Yamagishi A, Sato K, Miyashita M, et al (2014) Changes in quality of care and quality of life of outpatients with advanced cancer after a regional palliative care intervention program. J Pain Symptom Manage 48:602–610.

45. Zimmermann C, Swami N, Krzyzanowska M, et al (2014) Early palliative care for patients with advanced cancer: a cluster-randomised controlled trial. The Lancet 383:1721–1730.

46. Jordhøy MS, Fayers P, Loge JH avard, et al (2001) Quality of life in palliative cancer care: results from a cluster randomized trial. J Clin Oncol 19:3884–3894.

47. Bakitas M, Lyons KD, Hegel MT, et al (2009) Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial. JAMA 302:741–749.

48. Aaronson NK, Ahmedzai S, Bergman B, et al (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85:365–376.

49. Cella D, Nowinski CJ (2002) Measuring quality of life in chronic illness: the functional assessment of chronic illness therapy measurement system. Arch Phys Med Rehabil 83:S10–S17.

50. Webster K, Cella D, Yost K (2003) The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system: properties, applications, and interpretation. Health Qual Life Outcomes 1:79.

51. Cella DF, Tulsky DS, Gray G, et al (1993) The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol 11:570–579.

52. Lyons KD, Bakitas M, Hegel MT, et al (2009) Reliability and Validity of the Functional Assessment of Chronic Illness Therapy-Palliative Care (FACIT-Pal) Scale. J Pain Symptom Manage 37:23–32. doi: 10.1016/j.jpainsymman.2007.12.015

53. Cella DF, Bonomi AE, Lloyd SR, et al (1995) Reliability and validity of the functional assessment of cancer therapy—lung (FACT-L) quality of life instrument. Lung Cancer 12:199–220. doi: 10.1016/0169-5002(95)00450-F

54. Peterman AH, Fitchett G, Brady MJ, et al (2002) Measuring spiritual well-being in people with cancer: The functional assessment of chronic illness therapy—spiritual well-being scale (FACIT-Sp). Ann Behav Med 24:49–58. doi: 10.1207/S15324796ABM2401_06

55. Steinhauser KE, Clipp EC, Bosworth HB, et al (2004) Measuring quality of life at the end of life: Validation of the QUAL-E. Palliat Support Care 2:3–14. doi: 10.1017/S1478951504040027

56. Cohen SR, Mount BM, Strobel MG, Bui F (1995) The McGill Quality of Life Questionnaire: a measure of quality of life appropriate for people with advanced disease. A preliminary study of validity and acceptability. Palliat Med 9:207–219.

57. Browne JP, O'boyle CA, McGee HM, et al (1997) Development of a direct weighting procedure for quality of life domains. Qual Life Res 6:301–309.

58. Bertil Axelsson P-OS (1999) Assessment of Quality of Life in Palliative Care: Psychometric Properties of a Short Questionnaire. Acta Oncol 38:229–237. doi: 10.1080/028418699431663

59. Cohen SR, Boston P, Mount BM, Porterfield P (2001) Changes in quality of life following admission to palliative care units. Palliat Med 15:363–371.

60. Gaertner J, Siemens W, Daveson BA, et al (2016) Of apples and oranges: Lessons learned from the preparation of research protocols for systematic reviews exploring the effectiveness of Specialist Palliative Care. BMC Palliat Care 15:43. doi: 10.1186/s12904-016-0110-y

61. Song F, Hooper L, Loke Y (2013) Publication bias: what is it? How do we measure it? How do we avoid it? Open Access J Clin Trials 2013:71–81.

62. Nipp RD, Currow DC, Cherny NI, et al (2015) Best supportive care in clinical trials: review of the inconsistency in control arm design. Br J Cancer 113:6–11.

63. Siouta N, Van Beek K, Van der Eerden ME, et al (2016) Integrated palliative care in Europe: a qualitative systematic literature review of empirically-tested models in cancer and chronic disease. BMC Palliat Care 15:56.

64. American Board of Internal Medicine (2008) Hospice & Palliative Medicine Certification Policies. http://www.abim.org/certification/policies/internal-medicine-subspecialty-policies/hospice-palliative-medicine.aspx. Accessed 1 Mar 2017

65. Duke-NUS Graduate Medical School (2011) Report on the National Strategy for Palliative Care. Singapore

66. Breuer B, Fleishman SB, Cruciani RA, Portenoy RK (2011) Medical oncologists' attitudes and practice in cancer pain management: a national survey. J Clin Oncol 29:4769–4775.

67. Weinstein MC, Skinner JA (2010) Comparative effectiveness and health care spending—implications for reform. N Engl J Med 362:460–465.

68. Burke LA, Ryan AM (2014) The complex relationship between cost and quality in US health care. Virtual Mentor VM 16:124–130.

69. World Health Organization (2002) National cancer control programmes: policies and managerial guidelines.

70. Hui D, Elsayem A, De La Cruz M, et al (2010) Availability and integration of palliative care at US cancer centers. Jama 303:1054–1061.

71. Wentlandt K, Krzyzanowska MK, Swami N, et al (2012) Referral practices of oncologists to specialized palliative care. J Clin Oncol 30:4380–4386.

72. Lynch T, Connor S, Clark D (2013) Mapping levels of palliative care development: a global update. J Pain Symptom Manage 45:1094–1106.

73. Meier DE, Beresford L (2008) Outpatient clinics are a new frontier for palliative care. J Palliat Med 11:823–828.

74. Levit L, Balogh E, Nass S, et al (2013) Delivering high-quality cancer care: charting a new course for a system in crisis. Inst. Med. Wash. DC

75. Lamas D, Rosenbaum L (2012) Painful Inequities — Palliative Care in Developing Countries. N Engl J Med 366:199–201. doi: 10.1056/NEJMp1113622

76. Campbell MK, Piaggio G, Elbourne DR, Altman DG (2012) Consort 2010 statement: extension to cluster randomised trials.

77. Morita T, Miyashita M, Yamagishi A, et al (2013) Effects of a programme of interventions on regional comprehensive palliative care for patients with cancer: a mixed-methods study. Lancet Oncol 14:638–646.

Table 1 Study characteristics of randomized controlled trials (RCTs) included in the review.

Study information	Study period	Recruitment procedures	Participants	Cancer type and treatment	Data collection and tools used	SPC delivery	Outcome
Bakitas et al 2009 USA **Randomization level**: patients **Blinding:** Yes **Stratification** [a]**:** Yes (by randomization scheme, disease and blocked within strata) **Multiple cites**	2003-2007	**Inclusion criteria:** within 8 - 12 weeks of a new diagnosis of gastrointestinal tract (unrespectable stage III or IV), lung (stage IIIB or IV non–small cell or extensive small cell), genitourinary tract (stage IV), or breast (stage IV and visceral crisis), lung or liver metastasis, estrogen receptor negative, human epidermal growth factor receptor 2 positive cancer. **Exclusion criteria:** a) impaired cognition (<17 on a modified Mini-Mental State Examination), b) an Axis I psychiatric disorder (schizophrenia, bipolar disorder), or c) active substance use.	**Eligible** [b]: 681 **Total sample**: 322 (47% of eligible) **Total IG** [c]: 161 (50% of total) **Age**: IG: M = 65.4 (10.3) CG [d]: M = 65.2 (11.7) **Gender**: 60.2% M (IG: 62.1% M CG: 58.2% M) Inpatients and outpatients	**Cite**: cancer of the gastrointestinal tract (41%), lung (36%), cancer of the genitourinary tract (12%), and breast (10%) **Metastatic**: NR **Stage**: III, IV **Previous treatment**: parenteral chemotherapy or radiotherapy. **Prognosis (T1):** approx. 1 year	**Endpoints**: HRQoL [e], symptom intensity, resource use, mood **Tool for HRQoL**: FACIT-Pal [f]	**Team:** Delivered by two advanced practice nurses with palliative care specialty training, a palliative care physician and a nurse practitioner. **Place:** inpatient shared medical appointment and telephone consultations.	⇧ Confirmed by intention-to-treat analyses (p = .02).
Jordhøy et al 2001 Norway **Randomization level**: Community healthcare districts (clustered)	1995-1999	**Inclusion criteria:** a) incurable malignant cancer diagnosis; b) life expectancy between 2 - 9 months; c) > 18 years old **Exclusion criteria:** NR	**Eligible**: NR **Total sample**: 434 **Total IG**: 235 (54.1%) **Age**: IG: M = 67 (15) [estimated] [h], CG: M = 67 (16.2)	**Cite**: gastrointestinal 41.70%, lung 11.98%, breast and female genitals 15.44%, prostate and male genitals 9.45%, kidney/vesical/urethra 6.68%, lymphomas 2.99%, skin 2.76%,	**Endpoints**: pain control, physical functioning, emotional functioning, psychological distress **Tool for**	**Team:** GP, community nurse, consultant nurse or physician **Place:** PC unit/clinic	–

Blinding: No **Stratification:** Yes **1 site (community healthcare districts clustered)** [g]			[estimated] **Gender**: 53.0% M [estimated] (IG: 56% M, CG: 49% M) Inpatients and outpatients (community)	other 8.99% **Metastatic**: Yes **Stage**: NR **Previous treatment**: NR **Prognosis (T1):** NR	**HRQoL**: EORTC QLQ C-30 [i]		
Ozcelik et al 2014 Turkey **Randomization level**: patients **Blinding:** No **Stratification:** Yes (by age, gender and education level) **1 site**	2009-2011	**Inclusion criteria:** a) 'patients with an acute need for PC; b) > 18 years old; c) fully conscious cooperative and oriented; d) no sight or hearing problems; e) capable of verbal communication; f) diagnosed with advanced stage of cancer; g) prognosis 6-12 months; h) KPS [j] ≤ 50; i) with 1 or more uncontrollable symptoms; j) receiving PC **Exclusion criteria:** NR	**Eligible**: NR **Total sample**: 44 **Total IG**: 22 (50% of total) **Age**: IG: M = 52.6 (13.3), CG M = 53.6 (12.3) **Gender**: IG: 18.2% M, CG: 31.8% M Inpatients	**Cite**: gastrointestinal, genitourinary, breast, sarcoma, lung, and unknown primary tumour. **Metastatic**: Yes **Stage**: IV **Previous treatment**: NR **Prognosis (T1):** 6-12 months	**Endpoints**: HRQoL, symptoms, general and functional status, patient satisfaction, patient expenditure **Tool for HRQoL**: EORTC QLQ C-30	**Team**: Case Management nurse, Case Management team (RN Case Manager, oncologist, dietician, psychiatrist, social worker and physiotherapist), service nurses, consultation and with other specialties as well. **Place**: PC unit/clinic.	⇧ Role, emotional, social and global scores – Physical and cognitive functioning.
Temel et al 2010 USA **Randomization level**: patients	2006-2009	**Inclusion criteria:** a) have pathologically confirmed metastatic non-small-cell lung cancer; b) diagnosed the previous 8 weeks; c) ECOG [k] performance status 0,1,2; d) sufficient English literacy. **Exclusion criteria:** patients	**Eligible**: 283 (calculated by the Suppl. Appendix I) **Total sample**: 151 (74.2% of eligible) **Total IG**: 77 (51% of total)	**Cite**: non-small-cell lung cancer (100%) **Metastatic**: Yes (brain metastases in 31% of IG and 26% of CG) **Stage**: NR	**Endpoints**: HRQoL (Trial Outcome Index which is the sum of scores of LCS and the physical and functional wellbeing of the FACT-L), mood,	**Team:** Palliative care physician and advanced practice nurse (additional visits by the palliative care service – not specified what they entail).	⇧ Clinically meaningful improvements

Blinding: No **Stratification:** Yes (matched per demographics and prognostic factors balanced) **1 site**		already receiving PC.	**Age**: IG: M = 64.98 (9.73), CG: M = 64.87 (9.41) **Gender**: 58.3% M (IG: 51% M, CG: 45% M) Outpatients	**Previous treatment**: platinum-based chemotherapy, single agent, oral EGFR, tyrosine kinase inhibitor, radiotherapy, chemaradiotherapy, initial chemotherapy in 21% of IG and 27% of CG **Prognosis (T1):** NR	use of health services and end-of-life care **Tool for HRQoL**: FACT-L $_{l}$ + the lung subscale (LCS)	**Place:** Home-care visits	
Zimmermann et al 2014 Canada **Randomization level**: Oncology clinics (clustered) **Blinding:** No (but participants in study arms were not aware of the existence of the other arm – common method in cluster-randomized trials [76]AM **Stratification:** Yes (by clinic size and cancer site)	2006-2011	**Inclusion criteria:** a) > 18 years old; b) stage IV cancer; c) receiving refractory to hormonal therapy; d) stage III and poor clinical diagnosis at the discretion of the oncologist; e) estimated prognosis 6-24 months; f) ECGO performance 0, 1 or 2. **Exclusion criteria:** a) insufficient English literacy; b) inability to pass cognitive screening test (Short-Orientation-Memory-Concentration Test Score < 20 or > 10 errors).	**Eligible**: 992 (350 declined, 181 did not complete baseline assessment) No report of differences with those who were not enrolled) **Total sample**: 461 (46.4% of eligible) **Total IG**: 228 (49.5% of total) **Age**: IG: M = 61.2 (12), CG: M = 60.2 (11.3) **Gender**: 43.4% M (IG: 40.4% M, CG: 46.4 % M)	**Cite**: lung (21.9%), gastrointestinal (30.2%), genitourinary (16.9%), breast (15.6%), gynecological (15.4%) **Metastatic**: NR **Stage**: III, IV **Previous treatment**: chemotherapy (76.3% of IG and 78.1% of CG), radiotherapy (7 % of IG and 5.6% of CG) **Prognosis (T1):** 6-	**Endpoints**: HRQoL (primary); symptom control, satisfaction with care, problems with medical interaction (secondary) **Tool for HRQoL**: FACIT-Sp $_{m}$, QUAL-E $_{n}$	**Team:** Palliative care physician and palliative care nurse (for outpatient clinics and hospital services) with additional personnel for home care (personal support, physical therapy and occupational therapy). **Place:** PC unit/clinic and home-care visits	At 3 months ⇧ With QUAL-E – With FACIT At 4 months ⇧ With QUAL-E ⇧ With FACIT

		24months
1 site (24 oncology clinics)	Inpatients and outpatients (clinics and home care)	

Notes: a. Stratification in a cluster RCT can refer to cluster characteristics like for example the clinic size in the Zimmermann study. b. Eligible is considered the people assessed for eligibility excluding those who were excluded based on the exclusion/inclusion criteria. c. IG: Intervention Group. d. CG: Control Group. e. HRQoL: Health-Related Quality of Life. f. FACIT-pal: Functional Assessment of Chronic Illness Therapy-Palliative care subscale. g. Community health care districts were stratified into pairs according to their number of inhabitants older than 60 and to whether they represented rural or urban areas. Eligible patients were assigned treatment according to the cluster-district in which they lived h. Information was estimated and was not reported. i. EORTC QLQ C-30: European Organization for Research and Treatment of Cancer quality of life scale. j. KPS: Karnofsky Performance Scale. k. ECOG: Eastern Cooperative Group Score. l. Functional Assessment of Cancer Therapy-Lung subscale. m. Functional Assessment of Chronic Illness Therapy-Spiritual wellbeing subscale. n. Quality of Life at the End of Life questionnaire.

Table 2 Study characteristics of on-randomized controlled trials (RCTs) included in the review.

Study information	Study period	Recruitment procedures	Participants	Cancer type and treatment	Data collection and tools used	SPC delivery	Outcome
Bischoff et al 2013 USA **1 site**	2007-2010	**Inclusion criteria:** patients with any cancer diagnosis, stage, or oncologic treatments **Exclusion criteria:** patients who had palliative care follow-up within 120 days of their initial visit.	**Eligible** [a]: 574 **Total sample**: 266 (46.3% of eligible) **Age**: M = 57.2 (13.8) **Gender**: 46% M Inpatients	**Cite**: prostate (20%), Breast (19%), gastrointestinal (15%), gynaecologic (12%), head and neck (8%), non-prostate genitourinary (8%), lung (7%) **Metastatic**: Yes (59%) **Stage**: NR **Previous treatment**: 68% on active oncologic treatment **Prognosis (T1):** NR	**Endpoints**: HRQoL, patients' symptoms **Tool for HRQoL**[b]: Edmonton Symptom Assessment System (ESAS) questionnaire, one question from the QUAL-E survey ('How would you rate your overall quality of life?')	**Team:** Oncologists, palliative care physicians and an interdisciplinary team including a social worker, psychologist, nutritionist and a chaplain available for visits as needed by each patient. **Place:** PC unit/clinic	**First follow-up** ⇧ 0.26-point improvement (95 % CI 0.09–0.42; p = 0.002) **Second follow-up** ⇧ 0.33-point improvement (95 % CI 0.10–0.56; p = 0.02).
Cohen et al 2001 Canada **Multiple sites**	NR	**Inclusion criteria:** a) sufficient English or French literacy; b) a life expectancy ≥ 10days; c) sufficient physical stamina to allow participation; d) mental acuity sufficient for informed consent and questionnaire completion; e) ≥18 years old	**Eligible**: 194 **Total sample**: 135 (69.6% of eligible) **Age**: M = 64.0 (no SD reported, range 46-90) **Gender**: 49% M Inpatients	**Cite**: Most frequent reported: lung (12.6%), head and neck (8.9%), gastrointestinal (8.1%) **Metastatic**: NR **Stage**: NR **Previous treatment**: NR **Prognosis (T1):** NR	**Endpoints**: HRQoL **Tool for HRQoL**: McGill Quality of Life Questionnaire	**Team:** NR **Place:** NR	⇧ MQOL-SIS, MQOL total, physical symptoms, psychological, existential, and physical wellbeing.

		Exclusion criteria: NR					
Echteld et al 2007 The Netherlands **1 site**	2004-2005	**Inclusion criteria:** a) sufficient Dutch literacy; b) no limitations of consciousness (i.e. somnolence); c) no cognitive deficits (i.e. resulting from cerebral damage); d) likely admission duration of one week or longer (physician's estimate). **Exclusion criteria:** NR	**Eligible**: 60 **Total sample**: 29 (pre-intervention), 16 (post-intervention). **Age**: Pre-intervention: M = 55.3, Post-intervention: M = 60.6. **Gender**: Pre-intervention: 31% M, Post-intervention: 31.3% M Inpatients	**Cite**: Lung (20.7%), breast (13.8%), colorectal (13.8%), melanoma (10.3%), sarcoma (6.9%), urogenital for women (6.9%), urogenital for men (3.4%), unknown primary site (24.1%) **Metastatic**: NR **Stage**: NR **Previous treatment**: NR **Prognosis (T1):** NR	**Endpoints**: HRQoL, pain, fatigue, reconceptualization of cues. **Tool for HRQoL**: Schedule for the Evaluation of Individual Quality of Life	**Team:** Two nurse coordinators **Place**: PC unit/clinic	⇧ ES = 0.60
Melin-Johansson et al 2010 Sweden **1 site**	2003-2005	**Inclusion criteria:** a) patients who were aware of diagnosis and prognosis; b) ≥ 18 years old; c) sufficient Swedish literacy; d) ability to complete questionnaires independently; e) intended place of care: private homes **Exclusion criteria:** a) prognosis of less than 1month, as estimated by the team; b) other diagnoses than cancer; c)	**Eligible**: 163 **Total sample**: 63 (38.7% of eligible) **Age**: Mdn=72 (range 24-90) **Gender**: 57.1% M Outpatients	**Cite**: prostate (28.7%), lung (11.1%), breast (6.3%), stomach (9.5%), colon (19%), gynaecological (6.3%), liver (3.2%), other (15.9%) [percentages estimated not reported] **Metastatic**: Yes **Stage**: NR (incurable cancer) **Previous treatment**: NR **Prognosis (T1):** NR	**Endpoints**: HRQoL **Tool for HRQoL**: Assessment of Quality of Life at the End of Life (AQEL) (α = 0.74)	**Team:** Seven full-time registered nurses and two part-time physicians with specific training in palliative care and long clinical experience of caring for this population **Place:** Home-care visits	⇧ Global QoL – Social and existential domains.

		failing to give informed consent					
Stromgren et al 2005 Denmark **1 site**	1998-2000	**Inclusion criteria:** a) referred for symptom control, b) advanced stage cancer with no curative treatment options, c) with 'pronounced palliative needs., d) Danish speaking, e) ≥ 18 years, f) able to give consent. **Exclusion criteria:** NR	**Eligible**: 267 **Total sample**: 175 (65.5% of eligible) **Age**: Mdn = 63 (range 37-91) **Gender**: 44% M Inpatients and outpatients	**Cite**: head and neck (4.6%), gastrointestinal tract (20.6%), respiratory system (26/3%), breast (17.1%), genitourinary (16.6%), gynecologic (6.9%), sarcoma (1.1%), melanoma/skin (2.9%), hematologic (1.1%), unknown (2.9%). **Metastatic**: Yes **Stage**: NR (incurable cancer) **Previous treatment**: NR **Prognosis (T1):** Mdn = 35 days (range 3-1217 days)	**Endpoints**: HRQoL, anxiety, depression, orientation, memory, attention. Fatigue. **Tool for HRQoL**: EORTC QLQ C-30, ESAS	**Team:** Physicians (oncology, anesthesiology, internal medicine), nurses, social workers, chaplains, psychologists, physical therapists and dieticians **Place:** PC unit/clinic	⇧ Global QoL, nausea/vomiting, pain, lack of appetite, sleeplessness, constipation.
Yamagishi et al 2014 Japan **Multiple sites (4 regions)**	2008-2011	**Inclusion criteria:** a) adults with metastatic or recurrent cancer; b) outpatient visits to the oncology or each specialty division; c) the patient had been informed of the malignancy. **Exclusion criteria:** a) inability to complete the questionnaire (dementia, cognitive failure, psychiatric illness,	**Eligible**: 1488 (pre-intervention), 1501 (post-intervention) **Total sample**: 859 (pre-intervention, 57.7 % of eligible), 857 (post intervention, 57.1% of eligible) **Age**: Pre-intervention: M = 67.0 (11.0), Post-intervention: M = 68.0 (11.0)	**Cite**: Lung (26%), breast (16%), colorectal (14.5%), prostate, kidney, and bladder (14.5%), stomach and esophagus (10%), liver, bile duct, and pancreas (10%), uterus and ovary (6%) **Metastatic**: Yes **Stage**: NR (Advanced) **Previous treatment**: Chemotherapy and radiotherapy	**Endpoints**: Home death, use of a palliative care service, and patient-reported and bereaved family-reported quality of palliative care. **Tool for HRQoL**: Good Death Inventory, Care Evaluation Scale	**Team:** NR But methodological paper indicates that a clinician, a nurse, and a medical social worker were delivering the intervention. **Place:** Community-based	–

	language difficulty, or visual loss); b) severe emotional distress as determined by the principal treating physicians; c) poor physical condition	**Gender**: Pre-intervention: 55% M, post-intervention: 60% M Outpatients	**Prognosis (T1):** NR

Notes: a. Eligible are considered the people assessed for eligibility excluding those who were excluded based on the exclusion/inclusion criteria. b. HRQoL: Health-Related Quality of Life.

Table 3 Description of intervention and control procedures of included studies in the review

Study	Intervention name	Intervention background (i.e. theoretical)	Training towards people delivering the intervention	Duration of intervention	Intervention group procedures	Control group procedures
Bakitas et al 2009 USA	ENABLE (Educate, Nurture, Advise, Before Life Ends)	Palliative care is based on the chronic care model, using a case management, educational approach to encourage patient activation, self-management, and empowerment. Authors refined and converted the in-person and group strategies used in their previous studies. The intervention emphasized the importance of patients taking an active role in openly communicating with family and the oncology team regarding their values, priorities, and treatment preferences.	NR	**No. of sessions**: 4 weekly educational sessions. Ongoing support and coaching of patients by telephone until death. **Follow-ups**: every 3 months until death **Follow-up time**: Mean follow-up months = 14.6 (12.8). **Total duration**: 4 years	Advanced practice nurse–administered, telephone-based, intensive curriculum, and ongoing assessment and coaching in problem solving, advance care planning, family and health care team communication strategies, symptom management and crisis prevention, and timely referral to palliative care and hospice resources. Intervention participants and their caregiver were invited to attend monthly group Shared Medical Appointments (SMAs) led by a certified palliative care physician and nurse practitioner. These appointments allowed participants and caregivers to ask questions about medical problems or related issues (i.e., symptom management, insurance, social services) and to have more in-depth discussions than is practical during typical clinic visits.	Received usual care: allowed to use all oncology and supportive services, without restrictions including referral to the institutions' interdisciplinary palliative care service.
Bischoff et al 2013 USA	None	NR	NR	**No. of sessions**: Visits scheduled as frequently as needed by the patients **Follow-ups**: 2 **Follow-up time**: 41 and 81 days after	Patients were typically referred to the palliative care clinic by an oncologist and were followed by their oncologists after referral. The palliative care team coordinated their care with the oncologist, rendering a system of palliative and oncologic co-management. Initial visits typically involved medication management for pain, mood, and fatigue; Detailed prognosis discussions and	N/A

				initial assessment **Total duration**: 120 days	advance care planning typically occurred during subsequent visits. Opioids, non-opioid analgesics, antidepressants, anxiolytics, psychostimulants, laxatives, and antiemetic were the most common medications prescribed. Symptom management medications were prescribed directly by the palliative care physician. The majority of patient care was done during clinic visits; however, patients were able to communicate.	
Cohen et al 2001 Canada	None	NR	NR	**No. of sessions**: NR **Follow-ups**: NR **Follow-up time**: NR **Total duration**: NR	NR	N/A
Echteld et al 2007 The Netherlands	None	NR	NR	**No. of sessions**: Daily until hospital discharge (1-2 weeks) **Follow-ups**: Daily until hospital discharge (1-2 weeks) **Follow-up time**: Daily **Total duration**: 1-2 weeks	The purpose of the Unit was to provide symptom control (primarily pain) to advanced cancer patients, and thus facilitate discharge after adequate levels of symptom control have been reached.	N/A
Jordhøy et al 2001	Palliative Medicine Unit (PMU)	NR	An educational program for the community	**No. of sessions**: NR **Follow-ups**: 7	Individual treatment plans were set up in a joint meeting between the patient, the informal caregiver, the general practitioner (GP), the	NR

Norway	program		professionals included bedside training and 6 to 12 hours of lectures every 6 months.	**Follow-up time**: first 6 months after trial entry (monthly) and 2 years **Total duration**: NR	community nurse, and a consultant nurse or physician from the PMU. Follow-up consultations by the GP and the community nurse were arranged according to the patients' needs and predefined minimum standards. Hospital service was offered on request and always at the PMU, that is, unless otherwise required for medical reasons (i.e., surgery). The PMU consultant team participated in the inpatient care, handled the PMU outpatient clinic, coordinated the follow-up, and was available to the community staff for supervision and advice and to join visits in the patient's home.	
Melin-Johansson et al 2010 Sweden	Palliative Homecare Teams (PHTs)	NR	NR	**No. of sessions**: NR **Follow-ups**: NR **Follow-up time**: NR **Total duration**: 2 weeks	The aim of the intention is to minimize patient and family suffering by delivering effective, individualized palliative care, to support the patient's wish to stay at home as long as possible and to maintain an acceptable level of HRQoL (5-days-a-week consultations). It is complementary to hospitalized care and community healthcare services. During evenings, nights and weekends the district nurses on call in the county were in charge of the care. Interventions at home visits could include intravenous fluid therapy, blood transfusions, chemotherapy and other forms of technical support. The team also used specific methods for symptom control (e.g. for pain) and provided psychological, social and emotional support.	N/A
Ozcelik et al 2014	None	Case Management palliative care	A mode of delivering the intervention is provided but no specific indication of	**No. of sessions**: NR **Follow-ups**: NR	Received symptom diagnosis at T1 and organized effective symptom management, psychosocial stress management, social support, care and training support and family	Assessment by oncologist who organized usual treatment care. Usual

Turkey			how the team was trained	**Follow-up time**: NR **Total duration**: NR	counseling services. Monitored by and discharged by the Care Team. The PC Protocol in Advance Care Planning was used.	nursing care provided. Clinic routines applied.
Strömgren et al 2005 Denmark	None	Referred to as SPC Unit for symptom control and end-of-life care planning.	NR	**No. of sessions**: 3 **Follow-ups**: 3 **Follow-up time**: 1 week **Total duration**: 3 weeks	NR	NA
Temel et al 2010 USA	None	Specific attention to assessing physical and psychosocial symptoms, establishing care goals, assisting with treatment decision-making and coordinating care based on patients' needs	The palliative care clinicians documented provision of care according to the National Consensus Project for Quality PC guidelines (Clinical Practice guidelines for quality palliative care 2009 ref 14). No other training reported.	**No. of sessions**: Average 4 (range 0-8) **Follow-ups**: 1 **Follow-up time**: 12 weeks (or at outpatient clinic visits within 3 weeks before or after the 12 week time point). **Total duration**: 12 weeks	Early palliative care integrated with standard oncologic care. Information provided in study's Suppl. Appendix I on components: illness understanding/education, symptom management, decision-making, coping with life threatening illness, referrals/prescription.	No meeting with PC services unless requested. Those who did were not assigned to the PC group but kept to initial group. Received standard oncologic care.
Yamagishi et al 2014 Japan	Japan Outreach Palliative care Trial of the Integrated Model (the OPTIM study)	NR But methodological paper [77] provides information that the intervention was based on a scoping literature review and some preliminary surveys and discussions (between	NR But methodological paper indicates that local leaders of the intervention received a 2-day workshop before the intervention, 25 meetings took place	**No. of sessions**: NR **Follow-ups**: NR **Follow-up time**: NR **Total duration**: NR	Comprehensive program covering four areas: 1) to improve the knowledge and skills of palliative care; 2) to increase the availability of SPC services for community patients; 3) to coordinate community palliative care resources; and 4) to provide appropriate information about palliative care to the general public, patients, and families.	N/A

		researchers and healthcare professionals in the study regions).	during the intervention and a community nurse followed up by phone and email. Local leaders were provided with palliative care manuals.			
Zimmermann et al 2014 Canada	None	Approach to care declared as multidisciplinary addressing physical, psychological, social and spiritual needs.	In Hospital Services formal 10-day training at opening for palliative care unit and continuous education offered to palliative care nurses. Also, a detailed report on intervention procedures is outlined.	**No. of sessions**: 4 monthly sessions (primary endpoint = month 3, secondary endpoint = month 4). **Follow-ups**: 4 **Follow-up time**: 1 month **Total duration**: 4 months	Outpatient clinics: structured symptom assessment, psychological assessment (including discussions around care goals, patient and family support needs, distress and coping), advanced care planning. Patients were routinely assessed by telephone follow-up by a nurse after each visit and 24-h on-call service provided by palliative care physicians. Hospital service: symptom assessment and follow-up by palliative care team when admitted to non-palliative care unit service, Home care: explained at first visit, reassessed at each visit. A home palliative care physician offered when ECOG performance status ≥3 or at request of patient.	No palliative care received but a referral initiated if requested. In which case they were offered same care with IG but not the same standardized monthly follow-up.

Table 4 Quality assessment of included studies in the review

Study	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Total Score
Bakitas et al	2	2	2	2	2	1	1	2	1	1	1	2	2	2	2	0	25/32 (78.1%)
Bischoff et al	2	2	NA	1	1	1	0	0	1	1	0	NA	1	NA	NA	NA	10/22 (45.5%)
Cohen et al	1	2	NA	0	2	1	0	0	0	1	0	NA	1	NA	NA	NA	8/22 (36.4%)
Echtlend et al	1	2	NA	0	1	1	0	1	0	1	1	NA	1	NA	NA	NA	9/22(40.9%)
Jordhoy et al	2	2	1	1	2	1	1	1	0	2	1	0	1	2	0	0	17/32 (53.1%)
Melin-Johansson et al	2	2	NA	1	2	1	0	1	1	1	2	NA	1	NA	NA	NA	14/22 (63.6%)
Ozcelik et al	2	2	1	1	2	0	1	2	0	2	1	0	1	2	0	0	17/32 (53.1%)
Stromgren	1	2	NA	1	2	1	1	1	1	2	2	NA	1	NA	NA	NA	15/22 (68.2%)
Temel et al	2	2	2	1	2	1	2	2	1	2	2	0	1	0	0	0	20/32 (62.5%)
Yamagishi et al	2	2	NA	1	1	1	0	1	0	1	0	NA	1	NA	NA	NA	10/22 (45.5%)
Zimmerman et al	2	2	1	2	2	1	2	2	1	2	1	0	2	2	1	2	25/32 (78.1%)

Notes: Scoring: 2 = well-covered criterion, 1 = moderately or poorly addressed, 0 = not addressed. NA = Not Applicable
Criteria used: A - Objectives and hypotheses, B - Baseline assessment, C – Selection bias, D - Intervention explained, E – Primary outcome measures, F – Confounding variables, G – Power, H – Adherence to protocol, I – Precision, J – Attrition, K – Differential attrition, L – Intention-to-treat analysis, M – Generalizability, N – Randomization: Sequence generation, O – Randomization: Allocation concealment, P – Blinding procedures.
NA = Non Applicable (these criteria are relevant only for Randomized-Controlled Trials).

Fig 1 Flow Diagram of study identification and selection

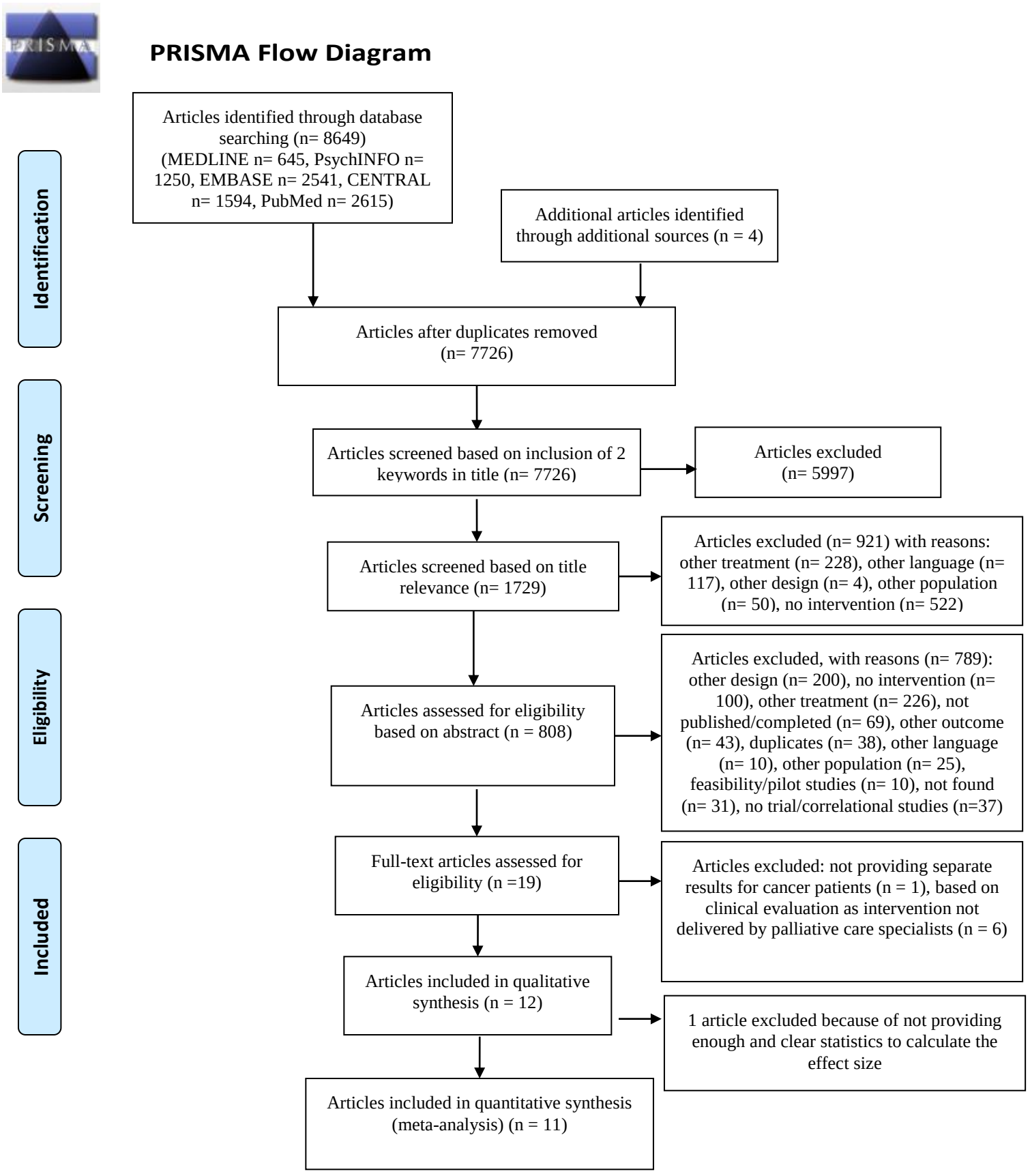
Fig 2 The attrition rates reported from baseline to end of study

Notes: Attrition for Yamagishi et al (2014) not reported since different participants responded to assessments pre- and post- the intervention. For Strömgren et al (2005) the 3rd week is used as T2 because the paper reports HRQoL changes in the 3rd week post- intervention.

Fig 3 Meta-analysis results of included studies

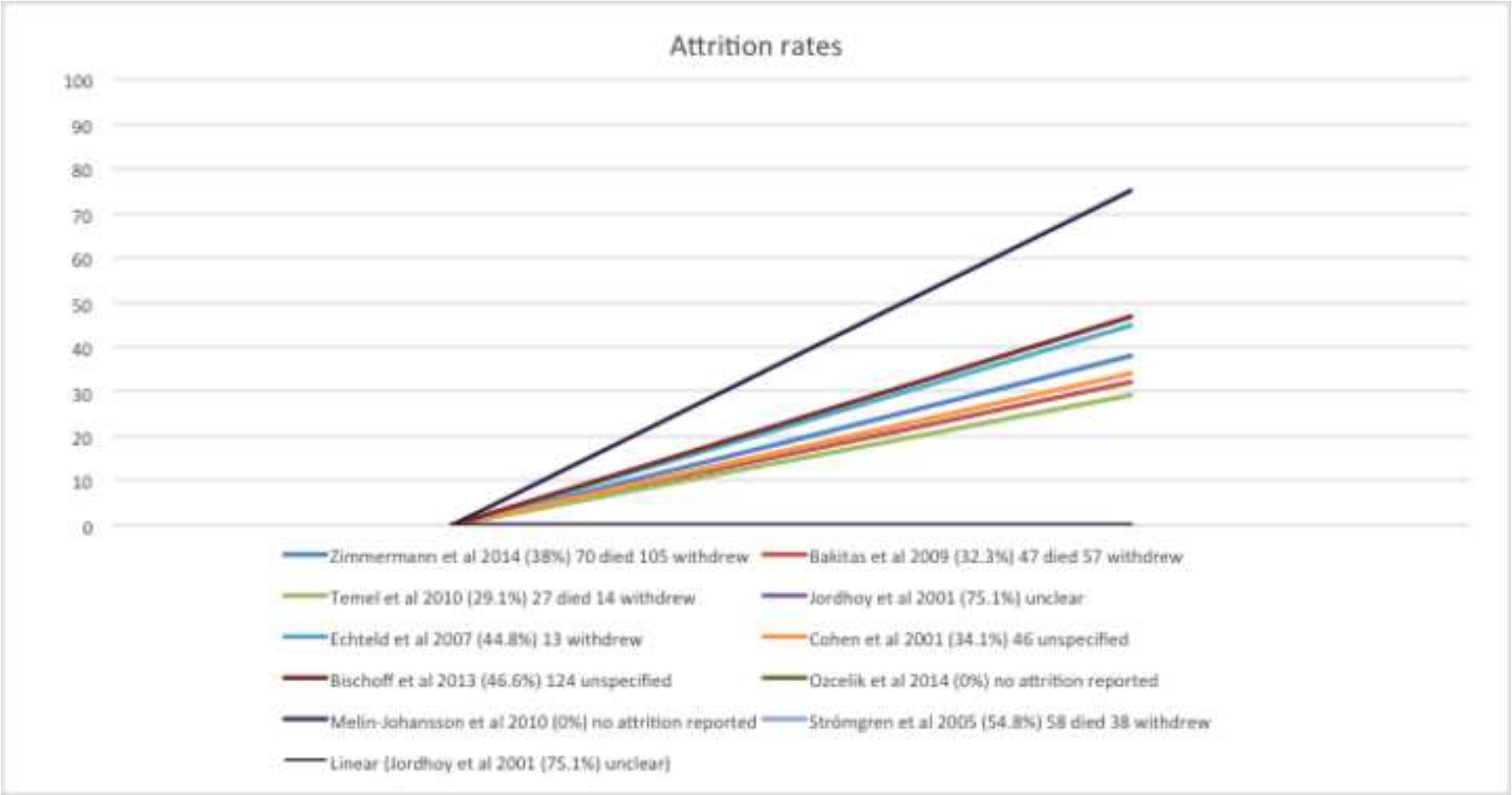
Notes: The figure presents the results of the meta-analysis favoring either the intervention or control arms of all studies, the RCTs only, or the non-RCTs only. Moreover, the funnel plot presents the publication bias of the included studies.

Figure


PRISMA Flow Diagram
Identification
Screening
Eligibility
Included
Articles identified through database searching (n= 8649) (MEDLINE n= 645, PsychINFO n= 1250, EMBASE n= 2541, CENTRAL n= 1594, PubMed n= 2615)
Additional articles identified through additional sources (n = 4)
Articles after duplicates removed (n= 7726)
Articles screened based on inclusion of 2 keywords in title (n= 7726)
Articles excluded (n= 5997)
Articles screened based on title relevance (n= 1729)
Articles excluded (n= 921) with reasons: other treatment (n= 228), other language (n= 117), other design (n= 4), other population (n= 50), no intervention (n= 522)
Articles assessed for eligibility based on abstract (n = 808)
Articles excluded, with reasons (n= 789): other design (n= 200), no intervention (n= 100), other treatment (n= 226), not published/completed (n= 69), other outcome (n= 43), duplicates (n= 38), other language (n= 10), other population (n= 25), feasibility/pilot studies (n= 10), not found (n= 31), no trial/correlational studies (n=37)
Full-text articles assessed for eligibility (n =19)
Articles excluded: not providing separate results for cancer patients (n = 1), based on clinical evaluation as intervention not delivered by palliative care specialists (n = 6)
Articles included in qualitative synthesis (n = 12)
1 article excluded because of not providing enough and clear statistics to calculate the effect size
Articles included in quantitative synthesis (meta-analysis) (n = 11)

Figure

Click here to download Figure Fig 2 .tiff



Figure

Click here to download Figure Fig 3_.tiff