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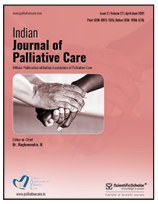

Review Article

Impact of Early Palliative Care to Improve Quality of Life of Advanced Cancer Patients: A Meta-Analysis of Randomised Controlled Trials

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ABSTRACT

Palliative care is often started late in patients with life-threatening conditions, particularly in patients with advanced cancer. However, with the emergence of the early palliative care (EPC) paradigm, their quality of life (QoL) may be better. Although several previous meta-analyses support the effectiveness of EPC in increasing QoL, essential issues related to the optimisation of EPC interventions are still needed. A systematic review and meta-analysis of randomised controlled trials (RCTs) were conducted to determine the effectiveness of EPC on the QoL of patients with advanced cancer. PubMed, ProQuest, MEDLINE through EBSCOhost and Cochrane Library and clinicaltrials.gov (register website) were searched for RCTs published before May 2022. Data synthesis used the Review Manager 5.4 to generate pooled estimates of effect size. A total of 12 empirical trials met the eligibility criteria and were included in this study. The results showed that EPC intervention had a significant effect (standard mean difference = 0.16, 95% confidence interval: 0.04, 0.28, Z = 2.68, $P < 0.05$). However, the secondary outcomes showed including mood (mean difference = −0.90, 95% CI: −2.32, 0.51, $P > 0.05$) and symptom controls (MD = −1.49, 95% CI: −3.81, 0.81, $P > 0.05$) had no significant effect. EPC is effective in improving the QoL of patients with advanced cancer. However, other outcomes still need to be reviewed, because the review of QoL is not enough to generalise the benchmarks for the effectiveness and optimisation of EPC interventions. Another notable aspect is to consider the most effective and efficient duration for starting and ending EPC interventions.

Keywords: Early palliative care, Quality of life, Mood, Symptoms, Advanced cancer, Meta-analysis

INTRODUCTION

In standard cancer care, palliative care is generally initiated when it is proven that disease-modifying treatment is not working, no treatment is available, or death is anticipated.[1,2] Meanwhile, early palliative care (EPC) starts much earlier in the course of the disease and is closer to the diagnosis of incurable cancer.[3]

As a new paradigm, EPC reduces the limitations of wider access to palliative care for patients with progressive and incurable cancer.[4] Patients with cancer who are newly diagnosed with advanced cancer on receiving initiation of palliative care will gain increased understanding of their prognosis.[5-7]

Some studies show that EPC is recommended, because it can affect the quality of life (QoL) compared to standard cancer care among patients with advanced cancer specifically for patients with solid tumours.[8-10] EPC is possible to affect the psychological, physical symptoms, proper relationships, effective communication and support in decision-making. However, the timing of EPC interventions continues to be debated and there is a lack of evidence needed for patients to introduce this approach by adjusting the individual situation to achieve patient expectations and a better QoL.[4]

The previous studies revealed a significant increase in QoL after receiving EPC. One recent study included symptoms, while another included symptom intensity as an outcome with non-significant results, but the results are inconclusive due to the low sample size, did not discuss the impact of EPC on QoL in general and did not involve recent studies.[3,11] Accordingly, a new study is needed to strengthen the evidence, whether the application of EPC is effective in improving the main outcome which is the QoL of patients with advanced cancer.

METHODS

Reporting standard

The Preferred Reporting Items for Systematic reviews and Meta-Analyses was used to conduct and guide the current review.

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Search strategies

A comprehensive literature search in the electronic database of PubMed, ProQuest, MEDLINE through EBSCOhost, Cochrane Library and clinicaltrials.gov (register website) was conducted in May 2022. The literature search was performed using keywords, subject headings (MeSH terms) and Boolean operators based on the PICO approach. Populations ('advanced cancer' OR 'metastatic cancer' OR 'metastatic neoplasms'), intervention ('early palliative care'), comparator ('standard oncology care') and outcome ('quality of life' OR 'symptoms' OR 'mood').

Study eligibility

The inclusion criteria were studies that: (a) Focused on adult patients (≥18 years) with advanced cancer/metastatic cancer, (b) randomised controlled trials (RCTs) assessing the effect of EPC in patients with cancer, (c) were originally published in English language and (d) outcomes of interest of patient with quality were QoL, symptom control and psychological issues. Studies that assessed EPC in populations other than patients with cancer, were systematic reviews, protocol studies and observational studies and had an outcome or/and intervention not appropriate were excluded from this study.

Study selection

Initial screening was done by two reviewers who independently screened potential titles and abstracts of relevant studies. The full text of the studies that met the inclusion criteria was retrieved and independently evaluated for inclusion by the three reviewers. Further, discussion was done to overcome any disagreement during study selection.

Data extraction

The three reviewers independently extracted the following information from each trial: first author, years publication, participants characteristic (sample size, age and cancer criteria), intervention characteristic (EPC and standard oncology care), measurement (instruments and time completion) and outcomes.

Quality assessment

The methodological quality of the included RCTs was assessed by three reviewers independently using the revised Cochrane risk-of-bias (RoB 2) tool to assess (RoB 2) in randomised trials.[12] We evaluated five domains of bias, including bias due to the randomisation process, bias due to deviations from the intended interventions, bias due to missing outcome data, bias due to measurement of the outcome and bias due to selection of the reported data.

Data synthesis and analysis

The Review Manager (RevMan) 5.4 version was used to perform all analysis (Cochrane Collaboration, http://ims.cochrane.org/revman). Heterogeneity was assessed using forest plots that used both Q (a significant result that indicates statistical heterogeneity)[13] and I^2 (a significant result that indicates methodological heterogeneity) statistics. Values of 25%, 50% and 75% indicate low, moderate and high heterogeneity, respectively.[14] A random-effects model was applied to calculate the pooled results if $I^2 \geq 50\%$; otherwise, a fixed-effects model was used. Forest plot graphics were generated to present the pooled effect. The standard mean difference (SMD) and mean difference (MD), with corresponding 95% confidence interval(CI), were used to calculate the effect size. SMD was calculated, where the same outcome was reported but using different measurement tools. All tests were two-sided and $P < 0.05$ was statistically significant.

RESULTS

Search process

After searching in the five databases and a trial register website, a total of 1213 articles were retrieved. For these articles, we conducted a duplicate check using reference manager (Endnote) either automatically or manually, preliminary screening (title and abstract) and full-text reading for screening. Finally, there were 12 papers with RCTs design that met the criteria of this meta-analysis. [Figure 1] shows the detailed search process and results.

Critical appraisal of quality

[Figure 2] shows the quality assessment of the included studies: 11 trials had low risk and one had some concern in the bias due to the randomisation process, eight trials had low risk and four had some concern in the bias due to deviation from intended intervention, ten trials had low risk and one had some concern in the bias due to missing outcome data, ten trials had low risk, one trials some concern and one had high risk in the bias due to measurement of the outcome. In terms of the bias selection due to selection report results, all included trials were of low risk. Overall, six trials were of low risk, four trials were of some concern and two trials were of high risk (one trial had bias due to the assessment of the outcome that was influenced by knowledge of the intervention received and one trial had bias in missing outcome due to high loss to follow-up rate during the intervention).

Included trials' characteristics

The essential characteristics of the included trials are shown in [Table 1]. In total, 12 trials assessing the impact of EPC intervention on patients with advanced cancer either solid or haematological cancer. Of the 12 trials, one trial was a cluster-RCTs,[15] two were multicentre-RCT,[16,17] and the others were parallel-RCTs.[18-25] The included trials were published from 2010 to 2022. The number of participants ranged from 120 to 461. EPC interventions were conducted in hospital and

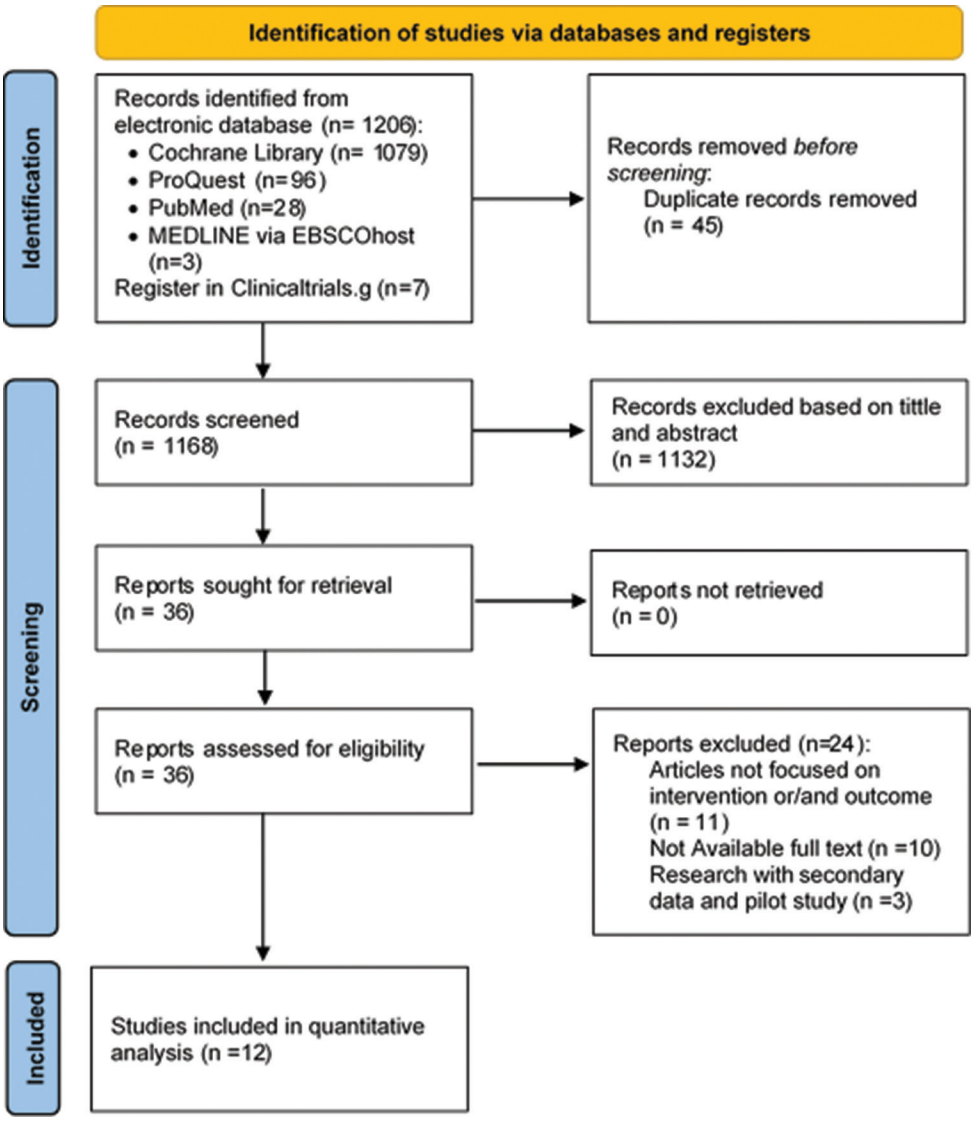

Figure 1: Flowchart for study selection according to PRISMA Declaration 2020. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

outpatient settings, involving oncologists, nurses and family members. All trials evaluated QoL as primary outcomes with several differences of tool measurement.

QoL meta-analysis

All trials evaluated the impact of EPC on QoL patients with advanced cancer. A total of 2364 participants were available for synthesis. For the EPC group compared with the standard care group, the result showed that EPC intervention had a significant effect (SMD = 0.16, 95% CI: 0.04, 0.28, Z = 2.68, $P < 0.05$; [Figure 3]). Heterogeneity was considerably moderate ($I^2 = 52\%$).

Mood meta-analysis

The outcome of mood was obtained from two trials and 447 participants were synthesised.[18,19] [Figure 4] indicates that the effect of EPC intervention on mood was not statistically significantly different (MD = −0.90, 95% CI: −2.32, 0.51, $P > 0.05$) and no heterogeneity was detected ($I^2 = 0\%$).

Symptom meta-analysis

The outcome of symptom was obtained from two trials and 507 participants were synthesised.[15,18] [Figure 5] indicates that the effect of EPC on symptoms had no significant effect (MD=−1.49, 95% CI: −3.81, 0.81, $P > 0.05$) and no heterogeneity was detected ($I^2 = 0\%$).

DISCUSSION

A meta-analysis of these 12 trials determined the effect of EPC interventions on patients with advanced cancer. This study reviewed and synthesised the effects of the EPC on the QoL, symptom control and mood in patients with advanced cancer.

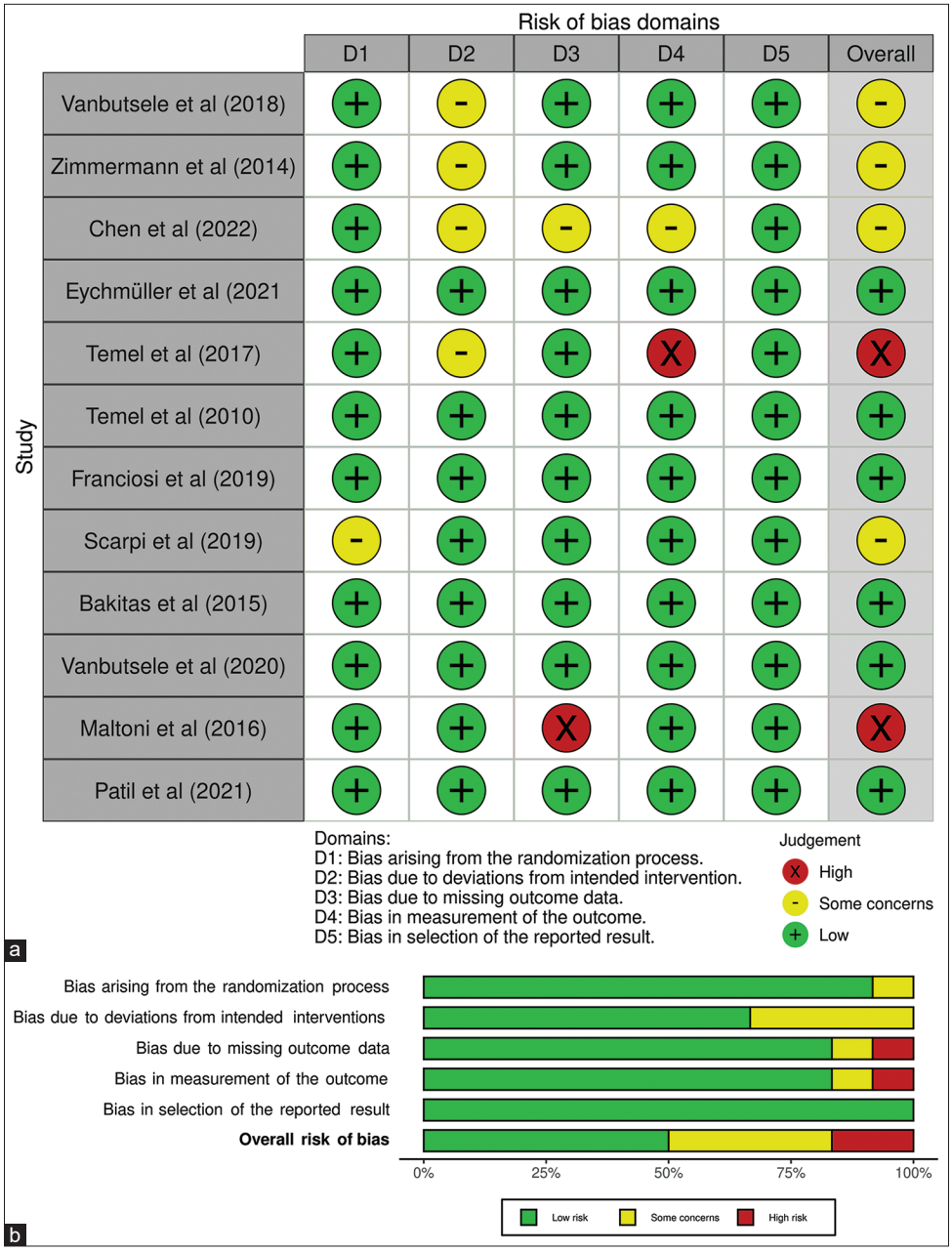

Figure 2: (a and b) Quality assessment of included trials.

The results revealed that QoL in the EPC group was significantly higher than in the standard cancer care. Compared to usual palliative care, initiating EPC or after diagnosis of advanced cancer is related to improving QoL, satisfaction with care and also improves patient understanding of their disease prognosis.[3,5,26] The results of Shih *et al.*[11] reveal a significantly higher overall QoL in the intervention group than in the control group at 3 and 6 months after the intervention. QoL in cancers with longer survival is better than those with shorter survival.[11] This varied nature may affect the effectiveness of EPC and maybe other aspects, because, in a previous study, there was evidence that there was no difference between the two study groups after 12 months received EPC.[27]

Whereas, in this study, the EPC did not improve some other outcomes such as symptom control. The most commonly identified symptoms are fatigue, excretory symptoms, urinary incontinence, asthenia, pain, constipation and anxiety which occur in at least half of patients.[28] Although the analysed research has used the same measurement instrument, it is necessary to review the age factor of the respondents. It is known that the mean age of the participants is ≥61 years.

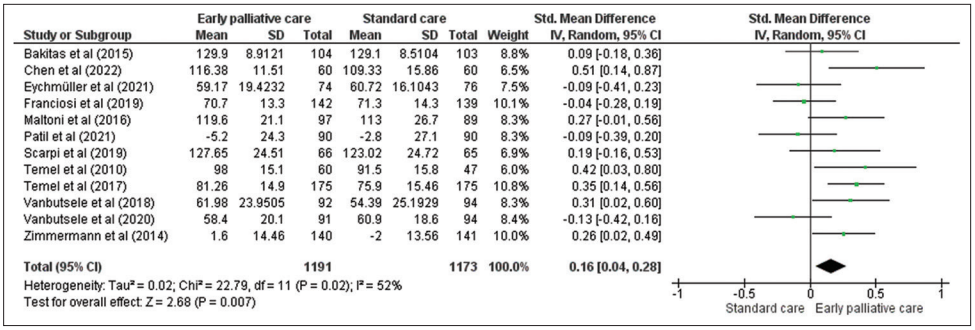

Figure 3: Forest plot for comparing early palliative care versus usual care; outcome: Quality of life.

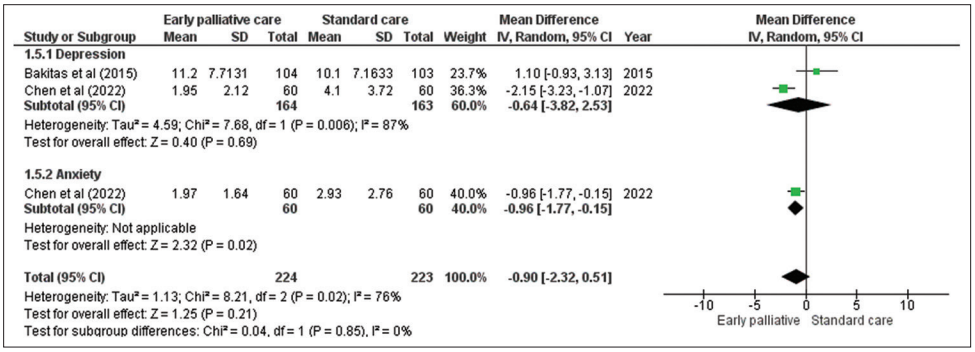

Figure 4: Forest plot for comparing early palliative care versus usual care; outcome: Mood.

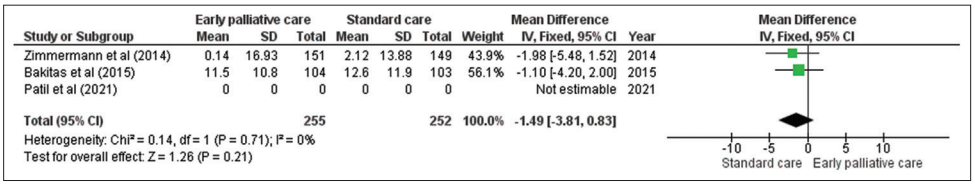

Figure 5: Forest plot for comparing early palliative care versus usual care; outcome: Symptom.

This is in line with the Van Lancker *et al.*[28] study, which found older palliative cancer patients suffered from various symptoms as the highest prevalence with high symptoms.

Others finding states that EPC is beneficial in symptom management of patients with advanced cancer and these findings are based on qualitative studies. Based on patient responses, EPC provides a sense of safety, support and affirmations and triggers structured action such as involving social networks.[29,30] It can lead to more consistent treatment with patient preference. Patients also want to focus on what is still possible, for example, cancer treatment and managing medical complications.[31]

Another finding is that EPC did not improve patients' mood. The findings from Holmenlund *et al.*[27] stated that there is moderate evidence that EPC can reduce psychological symptoms. Do Carmo *et al.*[32] stated that cancer is an incurable chronic disease, which can have an impact on all aspects of life and the patients are expected to show some psychological adjustment. This study found that symptoms of depression and anxiety will gradually improve, regardless of whether EPC is performed or not.

There are some differences contributing to the heterogeneity found in this study. The heterogeneity can be caused by the optimal timing of the EPC intervention for each article, where one article was conducted in several months, but another can be more optimal with a different timing.[15,18] The differences also involved the types of cancer and the use of different measurement instruments.[7,20] The advantage of our study is that the studies which we synthesised were articles published within a period of no more than 12 years. It provides some guarantee concerning the relevance of the data.

Limitations

There were some limitations in our study. We included all types of cancer in our participants, while cancer management can be different depending on the clinical characteristics of participants in included trials. In addition, no analyses were done on the impact of EPC based on the duration of the study, so we are not sure how long this EPC is effective and

Table 1: Characteristic of included trials.

Author (year)	Participant characteristic			Intervention	Control	Measurement	Main Outcome
	Sample size	Age (Mean±SD)	Advanced Cancer criteria				
Temel *et al.*[7]	*n*=350 (I: 175 C:175)	I: 64.03 (10.46) C: 65.64 (11.26)	Incurable lung (NSCLC, small-cell, or mesothelioma) or non-colorectal gastrointestinal	The core intervention of EPC was consultation and follow-up by a palliative care physician and nurse	Usual oncology care	FACT-G scale, PHQ-9; 3) The HADS	QoL, mood
Zimmermann *et al.*[15]	*n*=461 (I: 228 C: 233)	I: 61.2 (12.0) C: 60.2 (11.3)	Stage III and IV cancer	Consultation and follow-up in the oncology palliative care clinic by palliative care physician and nurse	Control group did not have the same standardised monthly follow-up.	FACIT-Sp, QUAL-E, ESAS	QoL, Quality of life in end of life, Symptoms
Maltoni *et al.*[16]	*n*=207 (I: 107 C: 100)	I: 67 (43–85) C: 66 (31–84)	Metastatic or locally advanced inoperable pancreatic cancer	EPC had an appointment scheduled with a PC specialist who had a predefined checklist of issues to be addressed during the consultation.	The standard arm was not scheduled to meet the PC team.	The FACT-Hep scale, The HADS	QoL, symptoms, mood
Franciosi *et al.*[17]	*n*=281 (I: 142 C: 139)	I: 68.5 (12) C: 68 (11)	NSCLC, pancreatic, gastric, or biliary tract cancer	The core intervention was consultation and follow-up by the Specialised PC Team	Standard treatments	FACT-G scale	QoL
Bakitas *et al.*[18]	*n*=207 (I: 104 C: 103)	I: 64.03 (10.28) C: 64.6 (9.59)	Advanced-stage solid tumour or hematologic malignancy	ENABLE a telehealth early PC model	Usual oncology care	FACIT-Pal, CES-D	QoL, mood
Chen *et al.*[19]	*n*=120 (I: 60 C: 60	I: 61.42±11.48 C: 64.62±10.50	Confirmed IIIB/ IV stage metastatic NSCLC	Early palliative care group integrated with standard oncologic care	Standard oncology care	FACT-L scale, The HADS	QoL, psychological state/mood
Vanbutsele *et al.*[20]	*n*=186 (I: 92 C: 94)	I: 64.5 (57.3-71.0) C: 65.0 (57.0–71.0)	Advanced cancer diagnosis a solid tumour	Systematic early integration of palliative care in oncological care	Usual oncological care	The EORTC QLQ C30	QoL
Vanbutsele *et al.*[21]	*n*=358 (I:91 C:94)	18–54 yo: I (19); C (18) 55–64 yo: I (43); C (46) 65–85 yo: I (29); C (32)	Advanced cancer with life expectancy of 12 months	Consultation with nurses from the PC team within 3 weeks of enrolment and monthly	Standard care without follow-up	The EORTC QLQ C30	QoL
Temel *et al.*[22]	*n*=151 (I:77 C:74)	I: 64.98±9.73; C: 64.87±9.41	Metastatic non-small-cell lung cancer	Comprehensive assessment and assisting with decision making.	Patient only met with the PC team on demand of the patient	FACT-L scale, The LCS	QoL, well-being
Patil *et al.*[23]	*n*=180 (I: 90 C:90)	I: 47.5 (40–57.3); C: 50 (42.7–57.3)	Patients with squamous cell carcinoma of the head and neck (Stage IV)	The EPC arm followed-up with the palliative care department every month for 3 months	Standard oncologic care	FACT-H&N, The ESAS-r	QoL, symptoms burden

(Contd...)

Table 1: (*Continued*)

Author (year)	Participant characteristic			Intervention	Control	Measurement	Main Outcome
	Sample size	Age (Mean±SD)	Advanced Cancer criteria				
Eychmüller *et al.*[24]	*n*=150 (I: 74 C: 76)	I: 67.3 (59.0±74.7); C: 67.3 (58.0±74.9)	Diagnosis of a tumour stage not amenable or not responsive to curative treatment	Early palliative care intervention	Usual oncology care	FACT-G; 2 The Palliative Care Outcome Scale	QoL, quality of care
Scarpi *et al.*[25]	*n*=186 (I: 66 C:65)	I: 70 (36–84); C: 69 (34–89)	Diagnosis of metastatic gastric cancer	Standard care plus systematic EPC	Standard care plus on-demand EPC	The FACT-Ga, TOI	QoL, TOI

EPC: Early palliative care, QoL: Quality of life, FACT-Ga: Functional assessment of cancer therapy-gastric, FACT-G: Functional assessment of cancer therapy-general, ESAS-r: Edmonton symptom assessment system-revised, FACT-H&N: Functional assessment of cancer therapy for head and neck cancer, LCS: Lung cancer subscale, EORTC QLQ C30: European organisation for research and treatment of cancer quality of life questionnaire, HADS: Hospital anxiety and depression scale, FACIT-Pal: Functional assessment of chronic illness therapy-palliative care, PHQ-9: Patient health questionnaire-9, FACT-G scale: Functional assessment of cancer therapy-general, ENABLE: Educate, nurture, advise, before life ends, TOI: Trial outcome index, FACT-L: Functional assessment of cancer therapy-lung, FACT-Hep: Functional assessment of cancer therapy hepatobiliary, FACIT-Sp: Functional assessment of chronic illness therapy – Spiritual well-being, QUAL-E: Quality of life at the end of life scale, ESAS: Edmonton symptom assessment system, FACT-H&N: Functional assessment of cancer therapy for head and neck cancer, CES-D: Centre for epidemiologic studies-depression scale

efficient to be done on patients with cancer and whether it follows their life expectancy or not.

CONCLUSIONS

The existence of this study is solely to strengthen and update the results of the previous studies and convince readers that the results of this study clearly demonstrate that EPC has been proven to be effective as an intervention that improves the QoL of patients with cancer, especially those diagnosed with advanced cancer. However, this study has not sufficiently proven that EPC also positively impacts patients' mood and symptom control during the intervention, so further research is needed.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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