




Economic Evaluation of Palliative Care for Patients with Cancer Disease: A Systematic Review

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Abstract

Background: With the increase in the population of cancer patients and the importance of reducing the economic burden of disease, it is very important to offer solutions that can provide the services needed by this group of patients in the most appropriate way. In recent years, palliative care services have been provided in a wide range of countries for this purpose, and many studies have been conducted to assess its economic and clinical aspects. The current study aimed to systematically review economic evaluation studies that investigate the costs of end-of-life care for cancer patients.

Methods: Electronic search was performed in multiple databases and different resources between 2000-2021 based on inclusion and exclusion criteria. Inclusion criteria were Studies consisting of a complete EE, including CEA, CUA, and CBA regarding the EE of palliative care for patients with cancer disease, EE studies carried out by decision analysis models following the EE approach, full-text articles in the English language, and published during 2000 and 2021 and According to our search strategy, the following articles were removed: studies conducted as a partial EE (like those intended to evaluate the effectiveness, cost evaluation, QoL evaluation), articles with poor methodological quality based on the CHEERS checklist, non-English studies, study protocols, articles presented to a conference, and letters to the editor. The quality of the articles was evaluated using a CHEERS checklist.

Results: 29 studies were included based on inclusion criteria. Most articles were published during the past decade. All studies were performed in high-income countries (UK= 6 studies, Canada= 5 studies). Most studies (n=7) focused on the health sector. Results of quality evaluation showed that 10 articles had excellent quality (score higher than 85%). Most studies (27 out of 29 studies) concluded that palliative medicine interventions were cost-effective and yielded positive cost-effectiveness results. 20 studies confidently concluded about the costs and benefits of providing palliative care services on cost-effectiveness and cost savings, and 2 studies made such a conclusion with uncertainty. Therefore, palliative care for cancer patients is cost-effective or cost-saving in 85% of studies.

Conclusion: Although there are a wide variety of studies, characteristics, and quality of the final studies included in the present study, there are relatively favorable and stable patterns regarding the results. Palliative care is usually less expensive than comparator groups, and the cost difference is statistically significant in most cases, and this treatment is a relatively cost-effective option. However, making the right relevant decision and applying it as a dominant therapy approach in different countries requires further study in larger populations and over a longer period.

Keywords: Cancer, Palliative medicine, Economic evaluation, Cost-effectiveness, Cost-utility

Conflicts of Interest: None declared

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↑What is “already known” in this topic:

Palliative care is specialized medical care for people living with a serious illness. This type of care is focused on providing relief from the symptoms and stress of the illness. The goal is to improve the quality of life for both the patient and the family.

→What this article adds:

This study indicated palliative care is usually less expensive than comparator groups, and the cost difference is statistically significant in most cases and improves the quality of life too. This treatment is a relatively cost-effective option.

Introduction

Globally, cancer is a major cause of death (1), so it claimed about 9.6 lives in 2018. In addition, about 18.1 million new cases were identified this year, according to the global cancer observatory (GLOBOCAN) (2). It is estimated that if cancer and population growth continue at the current rate, the incidence of cancer will reach 27.3 million worldwide by 2040. The disease is also recognized as a growing problem in Middle Eastern countries (2). Followed by cardiovascular diseases and traffic accidents, cancer is the third leading cause of death in Iran. The disease is often associated with pain, and pain is reported in approximately 50-70% of patients (3). Pain causes these patients to be hospitalized for a long time and incur huge costs (4). In recent years, the annual cost of treatment for each cancer patient has been estimated at 400,000 dollars, which means an annual out-of-pocket cost of 12,000 dollars per patient. According to the American Cancer Society, the cost of cancer-related health care in the United States was 87.8 billion dollars in 2014, and with an annual growth rate of 2%, this figure will reach 173 billion dollars by 2020. The total health care cost has been estimated at 1626 billion dollars in the United States, of which, 205 billion dollars (13%), is spent at the end of life (5). Estimates show that end-of-life health care costs account for 25% of medical costs in the United States. Also, it is estimated that approximately 20% of hospital beds in the UK are devoted to end-of-life care (6). It seems that efforts are made to reduce the health care costs of such patients by introducing new types of care and techniques.

Morrison et al. investigated the role of palliative care in reducing hospital costs compared to routine care and considered such care as an important factor in significantly reducing hospital costs for these patients (7).

World health organization (WHO) has identified palliative care as a solution to improve the quality of life (QoL) of cases with difficult to cure diseases and their families. This care begins with the diagnosis and continues throughout the disease course. These new interventions have significantly improved the survival and QoL of cancer people. Palliative care services have expanded worldwide to improve the end-of-life experience for patients with refractory diseases through better symptom control, care coordination, and improved communication between medical staff, the patient, and the patient's family. Palliative care promotes the QoL of those who suffer from life-threatening diseases as well as their families, and its purpose is to alleviate suffering by evaluating and relieving pain and other physical, psychological, social, and spiritual problems. Besides, many studies have reported the beneficial role of providing palliative care in the effectiveness and reduction of health care costs. For example, in a study of the effect of the palliative care hospital ward on costs, all cost reports in Thomas Smith et al.'s study have shown the usefulness and positive effect of such care in reducing hospital costs (8). However, there has been little development in the application of economic evaluation (EE) in this type of care as well as insufficient evidence in this

regard. There has also been no single technique of research methodology for the EE of such care and the results of such studies should be treated with caution (9). Following the collection of articles and evidence of huge costs, and considering the aforementioned issues, the importance of cancer and subsequent costs, and the need to improve the allocation efficiency of limited health system financial resources for cancer care, the present study conducted a systematic review of the EE of palliative medicine to identify the role of cost reduction and cost-effectiveness of palliative care interventions in cancer patients and thus to provide a reliable document for informed decisions in this area. The present study also sought to have a role in reducing the cost of cancer and improving overall health, and assisting health system policymakers in prioritizing and optimally allocating limited health resources.

Methods

Review of the literature

The present systematic review aimed to perform the EE of palliative medicine for cancer patients. The present study reviewed articles that included a complete economic evaluation (i.e., cost-effectiveness analysis (CEA) and cost-benefit analysis (CBA)) regarding systematic economic evaluation and EE of palliative medicine for cancer patients during the period 2000 to 2021. In order to find relevant studies, international databases, including Cinahl, PubMed, Scopus, web of science, Google scholar, Global Health, EconLit, Medline, and Embase, were used. The search strategy was designed by combining keywords. Search keywords, synonyms, and combining operators (OR and AND) were used to enhance the sensitivity of the search strategy.

Search process

Sample electronic search strategy in Pubmed database up to December 2021 was as follows:

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(((((cost effectiveness analysis[Title/Abstract]) OR cost utility analysis[Title/Abstract]) OR cost benefit analysis[Title/Abstract]) OR economic evaluation[Title/Abstract]) AND (((((((("Palliative Care"[Mesh]) OR Palliative care[Title/Abstract]) OR symptomatic treatment[Title/Abstract]) OR palliative radiotherapy*[Title/Abstract]) OR palliative medicine*[Title/Abstract]) OR palliative consult*[Title/Abstract]) OR Palliate*[Title/Abstract]) OR Palliative Surgery*[Title/Abstract]) OR Palliative Supportive Care[Title/Abstract]) OR Palliative Therapy*[Title/Abstract]) OR Palliative Treatment*[Title/Abstract])) AND (((neoplasm*[Title/Abstract]) OR tumor*[Title/Abstract]) OR cancer*[Title/Abstract]) OR malignant*[Title/Abstract]) OR "Neoplasms"[Mesh]).
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Inclusion criteria

Studies consisting of a complete EE, including CEA,

CUA, and CBA, regarding the EE of palliative care for the patient with cancer disease, EE studies carried out by decision analysis models following the EE approach, full-text articles in English language and published during 2000 and 2021.

Exclusion criteria

According to our search strategy, the following articles were removed: studies conducted as a partial EE (like those intended to evaluate the effectiveness, cost evaluation, QoL evaluation), articles with poor methodological quality based on the CHEERS checklist, non-English studies, study protocols, articles presented to a conference, and letters to the editor.

Quality assessment

The quality of the studies was assessed using the CHEERS instrument. This checklist includes 5 items with 24 indicators that are intended to evaluate the quality of EE articles concerning title and abstract/ background and description of the problem/ method/ findings and conclusion in a given country.

Study selection

All retrieved articles were entered into EndNote software. Afterward, duplications were identified and deleted. The rest were reviewed by two independent reviewers. Particular attention was paid to the PRISMA principles when identifying eligible articles. Initially, titles and abstracts were evaluated. Afterward, the full text of potentially relevant articles was obtained and reviewed. For all steps, the studies were reviewed by a third researcher in case of disagreement between reviewers.

Data extraction

For all articles that were found eligible for full-text review, a data extraction form was created in excel, which included author(s) name, publication year, country of origin, sample, cost-effectiveness, intervention, comparator, cost calculation basis, effectiveness calculation basis, and cost-effectiveness/cost saving.

Results

A total of 664 relevant studies were identified during the initial search. A total of 191 duplicate items were deleted. Of the remaining 473 studies, 289 were excluded due to having irrelevant titles and abstracts, and 184 relevant articles remained. After a full-text review, 98 articles were found as non-eligible. In total, 86 eligible articles were found. Among them, 40 were excluded because of insufficient and appropriate reporting of information or due being protocol. Twenty-nine full EE studies aimed at determining the costs and benefits of intervention versus a comparator were reviewed. The flow diagram shows the selection process according to the PRISMA statement (Fig. 1).

The quality of the reporting of 29 studies was evaluated in response to 24 questions from the CHEERS checklist (Table 1). Then, Scores 1 (✓), 0.5 (#), and 0 (×) were assigned to cases which were fully met, partially met, or never met in the study. The above quality was rated as excellent in 13 articles (higher than 85%), very good in 4 articles (75-85%), good in 12 articles (55-70%), and moderate in one article (55%). The results of evaluating the methodological quality of studies are provided based on the CHEERS checklist.

The characteristics of the selected studies are summarized in Table 2. The articles included in the final phase include the EE of the related intervention in a wide range of countries. Approximately all studies were performed in high-income countries, of which 6 studies were carried out in the United Kingdom (14, 18, 21, 24, 28), 4 studies in Canada (12, 13, 19, 31), and two studies in each of The United States (20, 34), Australia (22, 23), Greece (25, 26), and one study in each of Brazil (17), Italy (10), The Netherlands (29), France (11), New Zealand (15), Portugal (33), Sweden (30), Thailand (27) and Belgium (16). All studies have been performed on the homogeneous range of middle-aged patients with age-related risk factors, except for two studies performed on individuals aged 18 years and older (27, 29).

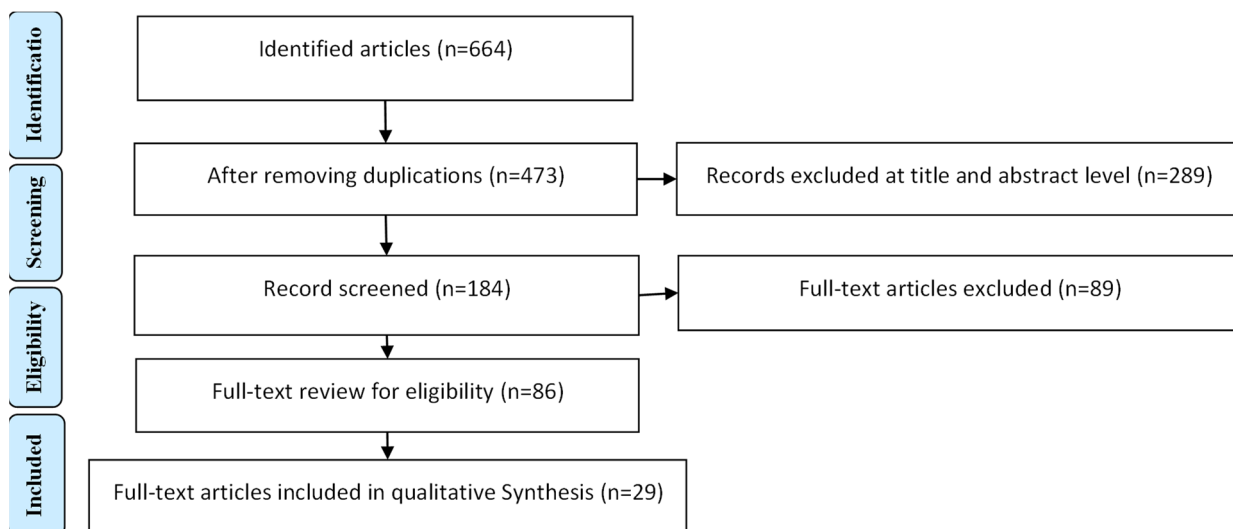


Fig. 1. Process of paper selection

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Table 1. CHEERS checklist: The methodological quality of articles

Rows	Authors/years	Title Identified as economic	Structured abstract	Intro provides context and a	Population characteristics	Setting and location	Study Perspective	Comparators described	Time horizon	Discount rate	Outcomes and relevance	Measurement of effectiveness	Pref based outcomes	Costs (unit costs and meth-	Currency, date and conversion	Model choice described	Model assumptions	Analysis methods	Parameters of values	Incremental costs	Sensitivity of incremental	Heterogeneity explained	Findings and limitations	Funding source	Potential conflict of interest	Total score	Total percentage
1	Bocci et al./2005 (10)	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✗	✗	✗	✗	✓	✓	✗	✓	✓	✗	17.5	73%	
2	Borget et al./2014 (11)	✓	✓	✓	✗	✓	✓	✓	✓	✗	✓	✓	✓	✓	✗	✗	✗	✗	✓	✓	✗	✓	✓	✓	18	75%	
3	Furlan et al./2012 (12)	✓	✓	✓	✗	✓	✓	✓	✓	✗	✓	✓	✓	✓	✗	✗	✗	✗	✓	✓	✗	✓	✓	✓	20	83%	
4	Coy et al./2000 (13)	✓	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✗	✗	✗	✓	✓	✓	✓	✓	✗	20	83%	
5	Burton et al./2007 (14)	✓	✓	✓	✗	✓	✓	✓	✓	✗	✓	✗	✗	✓	✗	✗	✗	✗	✓	✓	✗	✗	✗	✗	12	50%	
6	Collinson et al./2016 (15)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✗	✗	✗	✓	✓	✓	✓	✓	✓	19.5	81%	
7	Dooms et al./2006 (16)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✗	✗	✗	✓	✓	✓	✓	✗	✗	18.5	77%	
8	Da Silveira et al./2008 (17)	✓	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✗	✗	✗	✓	✓	✓	✓	✗	✗	18	75%	
9	Farquhar et al./2017 (18)	✓	✓	✓	✓	✓	✗	✓	✓	✗	✓	✓	✓	✓	✗	✗	✗	✗	✓	✓	✓	✓	✗	✗	18	75%	
10	Padula et al./2016 (19)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✗	✗	✗	✓	✓	✓	✓	✓	✗	23.5	98%	
11	Miller et al./2000 (20)	✗	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✗	✗	✗	✗	✓	✓	✗	✓	✗	✗	19.5	81%	
12	Meads et al./2019 (21)	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	22.5	94%	
13	McCaffrey et al./2013 (22)	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✗	✗	✗	✗	✓	✓	✓	✓	✓	✓	22	92%	
14	McCaffrey et al./2019 (23)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	24	100%	
15	Hopper et al./2004 (24)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	23	96%	
16	Tzala et al./2005 (25)	✗	✓	✓	✓	✓	✓	✓	✓	✗	✓	✗	✗	✓	✗	✗	✗	✗	✓	✓	✓	✓	✗	✗	15	62%	
17	Xinopoulos et al./2004 (26)	✓	✓	✓	✓	✓	✗	✓	✗	✗	✓	✓	✓	✓	✗	✗	✗	✗	✓	✗	✓	✗	✗	✗	13	54%	
18	Tanita et al./2018 (27)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✗	22	92%	
19	Shafiq et al./2015 (28)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	23	96%	
20	van den Hout et al./2006 (29)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✗	✗	✗	✓	✓	✓	✓	✓	✗	21	87%	
21	Wenger et al./2005 (30)	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✗	✓	✓	✓	✗	✗	✗	✓	✓	✓	✗	✗	✗	17.5	73%	
22	Thein et al./ 2017 (31)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	23	96%	
23	Round et al./2014 (32)	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✗	✗	✗	✗	✗	✗	✗	✓	✓	✓	✓	✗	✗	17	71%	
24	Araújo et al./2008 (33)	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	23	96%	
25	Abramson et al./2000 (34)	✓	✓	✓	✗	✓	✗	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	20.5	85%	
26	Halling et al./2020 (35)	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	✗	✗	✗	✓	✗	✓	✗	✓	✓	19	76%	
27	Adamson et al./2021 (36)	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	22	92%	
28	Chang et al./2020 (37)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	23	96%	
29	Beca et al./2020 (38)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	23	96%	

Table 2. Describing characteristics of cost-effectiveness studies

Row	Study	Country and year of publication	Model	Population	Alternative options for comparison	Outcome	Time horizon	Perspective	Considered cost	Sensitivity analysis	Discount rate	ICER
1	Bocci et al. (10)	Italy, 2005	-	64 patients with metastatic breast carcinoma	Low-dose cyclophosphamide-methotrexate 'metronomic' (CTX/MTX) therapy compared with novel chemotherapy strategies (phase II trials).	QALYs	17 months	National Health Service (NHS)	All direct costs	Probabilistic sensitivity analysis	-	Gemcitabine regimen (cost gained for progression-free life year e3 664), oxaliplatin/leucovorin/5-FU treatment (cost gained for progression-free life year e13 965), docetaxel/vinorelbine chemotherapy (cost gained for progression-free life year e17 560), and docetaxel/ carboplatin administration (cost gained for progression free life year e14 904) showed a small but favourable cost-effectiveness ratio in comparison with metronomic treatment.
2	Borget et al. (11)	French, 2014	-	834 patients who received induction chemotherapy	predefined second-line treatment after cisplatin-gemcitabine induction chemotherapy	QALYs	18 months	French health payer's perspective	Direct treatment costs (medicines, hospital admission, follow-up assessments, second-line therapies and palliative care)	One way and probabilistic sensitivity analysis (PSA)	-	The ICERs for gemcitabine or erlotinib maintenance treatments were 76,625 and 184,733 euros per QALY, respectively.
3	Furlan et al. (12)	Canada, 2012	Markov model	17000 patients with metastatic spinal cord compression	Radiotherapy	QALYs	60 Days	Ontario Ministry of Health and Long-Term Care	The costs of both therapies include physician fees and hospital bills.	1-way and 2-way sensitivity analyses, threshold analysis, and probabilistic sensitivity analysis	-	The ICER of S + RT compared with sole RT is US\$250 307.30.

Table 2. Continued

Row	Study	Country and year of publication	Model	Population	Alternative options for comparison	Outcome	Time horizon	Perspective	Considered cost	Sensitivity analysis	Discount rate	ICER
4	Coy et al. (13)	Canada, 2000	Cox proportional hazards model	162 patients with lung cancer	High-dose palliative RT compares with several other frequent strategies.	QALYs	1year	Clinic & societal perspective	In-clinic costs Assessment Planning Treatment Follow-up visits Social work visits Nutrition visits Total in-clinic costs Time/travel costs Non-clinic medical costs Total societal costs	Multivariate sensitivity analysis	0.05	Cost-effectiveness of high dose palliative RT vs. BSC is \$9245 per life year (LY) from the clinic's perspective, and \$12,253 from the societal perspective.
5	Burton et al. (14)	UK, 2007	Multiple imputation (MI)	115 patients with advanced non-small cell lung cancer	chemotherapy (CT) against standard palliative care Standard palliative care	QALYs	10 months	Decision-maker perspective	The total cost contained five categories. (i) medical costs (chemotherapy (CT) and radiotherapy (RT)); (ii) a Queen Elizabeth (QE) hospital cost, which participants were mostly found seen and treated (except for CT and RT costs); (iii) a non QE hospital cost, which contained costs at any other healthcare center that the participants referred after randomization; (iv) a community-based GP cost; and (v) a hospice cost.	-	-	CT can be cost-effective for a societal willingness to pay more than £20 000 per life-year gained.

Table 2. Continued

Row	Study	Country and year of publication	Model	Population	Alternative options for comparison	Outcome	Time horizon	Perspective	Considered cost	Sensitivity analysis	Discount rate	ICER
6	Collinson et al. (15)	New Zealand, 2016	Markov microsimulation model	patients with Stage IV metastatic breast, prostate and lung cancers	Single- and multiple-fraction external beam radiotherapy (SFX & MFX)	QALYs	lifetime horizon	Health system perspective	Health system costs	Univariate sensitivity analyses	0.03	For all three cancers, SFX was clearly more cost-effective than MFX.
7	Dooms et al. (16)	Belgium, 2006	Decision-analysis model	142 patients with advanced NSCLC	Cisplatin & Vindesine	QALYs	12 months	Societal perspective	Direct medical and non-medical costs, Indirect costs, Costs occurred after the end of the trial	Probabilistic sensitivity analysis	-	Incremental cost-utility ratio for gemcitabine of J13,836 per QALY gained.
8	Da Silveira et al. (17)	Brazil, 2008	Decision model	Patient with unresectable esophageal cancer	Self-expandable stent (SES), brachytherapy, and laser	QALYs	9 months	Third-party payer perspective	-	Probabilistic sensitivity analysis	-	In the as usual scenario, the laser had the least CE ratio, followed by brachytherapy at an ICER of \$4,400.00, and SES is a dominated intervention.
9	Farquhar et al. (18)	UK, 2017	linear regression model	44 patients with non-malignant conditions	Standard care	QALYs	2 months	-	Inpatient Other hospital services, GP, Nurse, Other health services, Social and other care	-	-	The ICER revealed that the strategy led to a cost per QALY of £266,333.
10	Padula et al. (19)	Canada, 2016	Decision trees	Use population health data	Resuscitate	QALYs	1year	Patient, provider and societal perspectives	-	Probabilistic sensitivity analysis	-	At a rate of survival less than 3.62%, the ICER for resuscitation.

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Table 2. Continued

Row	Study	Country and year of publication	Model	Population	Alternative options for comparison	Outcome	Time horizon	Perspective	Considered cost	Sensitivity analysis	Discount rate	ICER
11	Miller et al. (20)	USA, 2000	Decision-analytic model	68 patients with locally recurrent rectal carcinoma	1- Surgical resection 2- Palliative surgery	QALYs	4 years	Perspectives of patients and health care providers.	-	-	-	ICER of \$100,000/QALY.
12	Meads et al. (21)	UK, 2019	Markov cohort model	Patient with Advanced Cancer		QALYs	10 years	Health service provider	Only implementation costs are considered and those related to the development stage are removed.	One way and probabilistic sensitivity analysis (PSA)	0.035	TCPT had a lower prime cost (respective incremental costs - GBP148 [- EUR168.53] and - GBP474 [- EUR539.74]) and more effective (respective incremental QALYs of 0.010 and 0.013) compared to common care.
13	McCaffrey et al. (22)	Australia, 2013	Within-trial analysis	32 consented participants with predominantly advanced cancer	Palliative Care Extended Packages at Home (PEACH) and usual care.	QALYs	28 days	Healthcare provider perspective	Direct cost	Probabilistic sensitivity analysis	-	The findings of this small-scale pilot mentioned the potential of PEACH as a cost-effective end-of-life care model compared to common care.
14	McCaffrey et al. (23)	Australia, 2019	Within-trial CEA	185 Adults with refractory, chronic cancer pain	Subcutaneous ketamine versus placebo.	QALYs	5day trial period	Healthcare provider perspective	Direct costs	One-way sensitivity analyses	-	subcutaneous ketamine in conjunction with opioids and standard adjuvant treatment is neither an effective nor cost-effective strategy for refractory pain in patients with progressed cancer

Table 2. Continued

Row	Study	Country and year of publication	Model	Population	Alternative options for comparison	Outcome	Time horizon	Perspective	Considered cost	Sensitivity analysis	Discount rate	ICER
15	Hopper et al. (24)	UK, 2004	Hypothetical cohort model	Cases with progressed head and neck cancer	1- Palliative chemotherapy 2- Extensive palliative operation 3- No therapy	QALYs	10 years	Healthcare provider perspective	Direct cost	Robust sensitivity analyses	0.06	Foscan-PDT is a cost-effective therapeutic option for patients with progressed head and neck cancer in comparison with palliative chemotherapy, extensive palliative surgery, or 'no intervention'.
16	Tzala et al. (25)	Greece, 2005	Non-parametric bootstrap	55 hematological cancer patients	Conventional hospital care	QALYs	January to June 2002	Perspective of the hospital	-	One-way analysis and scenario analysis	-	The incremental cost was €522 (95% confidence interval: €516–528).
17	Xinopoulos et al. (26)	Greece, 2004	-	30 patients with inoperable malignant	Stoma creation	QALYs	Between March 1998 and April 2002	Health Care System	Average total cost	-	-	Self-expanding metallic stent placement is a better QoL, without the psychological repercussions of a colostomy, and it may be cost-effective.
18	Tanita et al. (27)	Thailand, 2018	Direct calculation and Markov decision analysis model	274 patients with hilar CCA	Palliative biliary drainage (EBD or PTBD)	QALYs	August 2011 to January 2015	Patient	Total lifetime cost	Probabilistic sensitivity analysis	-	The ICER from EBD and PTBD were 655.520 baht (US\$ 19.568) and 6,548,398 baht (US\$ 195,475) per QALY gained, respectively.
19	Shafiq et al. (28)	UK, 2015	Decision tree model approach	Medicare data were used	various palliative interventions, including repeated thoracentesis (RT), thoracoscopic talc poudrage (TP), talc slurry (TS), tunneled pleural catheter (TPC), and rapid pleurodesis protocol (RPP).	QALYs	6 months	Third-party payer & Medicare data were used	Intervention Total Cost	Multivariate sensitivity analysis	-	Previous research mostly used \$100,000/QALY in light of a more recent analysis (2009) that estimated dialysis' ICER as \$110,814/QALY in comparison to no dialysis.

Table 2. Continued

Row	Study	Country and year of publication	Model	Population	Alternative options for comparison	Outcome	Time horizon	Perspective	Considered cost	Sensitivity analysis	Discount rate	ICER
20	van den Houtet al. (29)	Dutch, 2006	-	303 cases with end-stage cancer of the esophagus or gastroesophageal junction.	10 fractions of 3 Gy (10 × 3 Gy) versus two fractions of 8 Gy (2 × 8 Gy).	QALYs	from January 1, 1999, to May 31, 2002	Societal perspective		Multivariate (non-random) sensitivity analysis	0.03	Compared with the 2 × 8 – Gy group, the 10 × 3 – Gy group accrued statistically significantly more QALYs.
21	Wenger et al. (30)	Sweden, 2005	Prospective randomized multicenter trial	65 Patients with incurable cancer of the esophagus or gastro-esophageal junction.	Stent placement versus brachytherapy as a palliative strategy.	QALYs	Between 1999 and 2002	-	Total lifetime costs contained health expenditures during the patient's life (i.e., costs for initial therapy, for all operation procedures and endoscopic interventions with extra charge if endoscopy was conducted using general anesthesia, for hospitalization, out-patient referral, for emergency department visits, for rehabilitation or hospice departments, for X-ray evaluations, for central venous catheters and for days on total parenteral nutrition).	Probabilistic sensitivity analysis	-	Currently stenting has higher cost-effectiveness than fractionated 3*7Gy brachytherapy for end-stage cancer patients of the esophagus and gastro-esophageal junction.
22	Thein et al. (31)	Canada, 2017	net benefit regression	1172 patients diagnosed with HCC	non-curative palliative treatment strategies such as TACE alone or TACE+ sorafenib, sorafenib alone, & non-sorafenib chemotherapy compared with no treatment or best supportive care (BSC).	QALYs	Between 2007 and 2010	Health care payers	The total health expenditures contained outpatient referrals, emergency ward visits, hospitalizations period, same-day operations, prescribed drugs, home care referrals, continuing care, and long-term healthcare services.	Published literature	0.03	ICER calculations for sole TACE or TACE+ sorafenib was \$6,665/QALY

Table 2. Continued

Row	Study	Country and year of publication	Model	Population	Alternative options for comparison	Outcome	Time horizon	Perspective	Considered cost	Sensitivity analysis	Discount rate	ICER
23	Round et al. (32)	London, 2014	within-trial stochastic CUA using Monte-Carlo simulation	41 people with advanced, progressive, recurrent cancer	Rehabilitation service, delivered in a hospice day care unit versus usual care.	QALYs	Between August 2010 and July 2011	NHS and personal social services	Total cost	Probabilistic sensitivity analysis (PSA) in a Bayesian framework	-	The ICER for the base scenario analysis was £14,231 per QALY.
24	Araújo et al. (33)	Portuguese, 2008	A three-stage model of health (free of progression; progression; death)	1457 cases with progressed or metastatic NSCLC (stages IIIA, IIIB, or IV) has at least one prior failed chemotherapy regimen	Docetaxel, Pemetrexed and best supportive care.	QALYs	2 years	Portuguese National Health System (NHS)	Total cost	Probabilistic sensitivity evaluation conducted by second-order Monte Carlo simulation 500 times.	0.05	the ICER between erlotinib and supportive care was higher than the €30 000 /QALY.
25	Abramson et al. (34)	USA, 2000	spreadsheet model	21 patients who underwent HACE	Hepatic arterial chemoembolization (HACE)	QALYs	From April 1996 through December 1998. (24 months)	payer	Marginal direct cost & Total direct costs	Probabilistic analysis.	-	The cost-effectiveness of HACE for treating CLM differs based on the estimated survival benefit.
26	Halling et al. (35)	Denmark, 2020	-	321 patients (162 in the intervention group, 159 in the control group) and 235 caregivers (126 in the intervention group, 109 in the control group)	Fast-track transition from oncological treatment at the hospital to SPC at home compared to usual care.	QALYs	6 months	Societal	The costs included primary and secondary healthcare costs, cost of intervention and informal care from caregivers.	Probabilistic sensitivity analysis	-	the ICER was €118,292/QALY when adjusting for baseline costs and quality of life.

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Table 2. Continued

Row	Study	Country and year of publication	model	population	Alternative options for comparison	Outcome	Time horizon	perspective	Considered cost	Sensitivity analysis	Discount rate	ICER
27	Adamson et al. (36)	UK,2021	combined decision tree and Markov model	199 Patients (aged ≥16 years) with incurable oesophageal carcinoma	adjuvant external beam radiotherapy (EBRT) compared with usual care alone	survival, quality of life (QoL), morbidities (including time to first bleeding event or hospital admission for bleeding event and first dysphagia-related stent complications or re-intervention) and cost-effectiveness.	12 Month	NHS and Personal Social Services perspective	Total cost	Probabilistic sensitivity analyses	-	No time versus treatment interaction was observed for prespecified QoL outcomes.
28	Chang et al. (37)	USA, 2020	A Markov model	1 million patients with uncomplicated painful bone metastases eligible for palliation were simulated	External Beam Radiation Therapy versus Percutaneous Image-Guided Cryoablation	QALYs	Lifetime	Payer	Medical costs	One-way and probabilistic sensitivity analyses	3%	Ablation-SFRT and ablation-MFRT were not cost-effective with ICERs>\$100,000/QALY.
29	Beca et al. (38)	Canada,2020	A Markov model	Patients with primary central nervous system lymphoma (PCNSL)	(1) progression-free survival (PFS), (2) salvage treatment, (3) palliative care and (4) death	QALYs	20 years	Health care system	Total cost	one-way sensitivity analysis	1.5%	Incremental cost-effectiveness ratio of \$24,758/QALY gained.

Three studies hold a social perspective that considers costs and benefits regardless of the people to whom these costs are imposed (13,16,29). Among the remaining studies, 7 articles from the health care system perspectives (10,12,26), 7 studies from the patient perspective (27), 3 studies from the payer perspective (11,26,31,34), 5 studies from the service provider perspective (21), 1 study from the hospital perspective (25), have analyzed the costs and benefits of palliative care and other studies did not specify the study perspective. A small number of studies lasted more than 3 years (15,20,21,24,26,27). Most of the studies that considered the annual interval was carried out in one or two-year periods, Therefore, so they have not used the discount rate to calculate costs and benefits, and a small number have used a discount rate of 3% (15,21). All interventions analyzed under the current situation (routine care) or a situation in which there is no comparative intervention, were evaluated. Some of these interventions include controlling and managing patients' pain through the use of analgesics, chemotherapy and radiotherapy, surgical procedures, home care, and hospital daycare. Among these studies, 14 studies analyzed cost-effectiveness (10,13,14, 15,17,19,22,23,24,31), 8 studies analyzed cost-utility (12,16,20,27,28,29,32), 2 studies analyzed cost-saving (25,33), and 1 study analyzed the palliative medicine costs (30).

Most studies (26 out of 29 studies) concluded that palliative medicine interventions were cost-effective and yielded positive cost-effectiveness results. 20 studies confidently concluded about the costs and benefits of providing palliative care services on cost-effectiveness and cost savings, and 2 studies made such a conclusion with uncertainty. When the palliative medicine method is measured by the willingness-to-pay criterion, it has been introduced as cost-effective, and it has not provided a definite opinion about the cost-effectiveness of palliative medicine for patients with heart disease also due to cost estimating uncertainty. Although palliative care intervention is cost-effective in some situations, there is a great deal of uncertainty about the decision to implement it (17,33). The results of three studies among the reviewed studies reveal a lack of cost-saving and cost-ineffectiveness in palliative medicine. These studies conclude that palliative care not only has no survival benefits but also imposes high costs compared to other conventional therapies (20).

Some studies have considered the use of palliative medicine as cost-effective in advanced stage and incurable cases of the disease, and it has been stated that the use of these methods will reduce costs and increase the QoL of patients with end-of-life symptoms (23,24).

In some cases, palliative medicine is cost-effective from the perspective of society and service providers, but such interventions are not cost-effective from the patients' perspective due to the risk of using new treatments and the desire to receive definitive treatments (19).

A number of studies have stated that palliative medicine intervention in cancer patients increases costs but have stated that the use of these methods will lead to improved treatment outcomes at the same time (12).

Discussion

The present study reviews the evidence regarding the EE of palliative medicine compared to conventional care or no treatment. Finally, 29 studies met the inclusion criteria. The quality of the final studies was at an acceptable level. Twenty studies have commented with certainty on the cost-effectiveness and cost-saving, and two studies have made uncertain comments in this regard. Moreover, the results of three studies among the reviewed studies demonstrated that palliative medicine doesn't reduce costs and is not cost-effective. These studies concluded that palliative care not only has no survival benefits compared to other conventional treatments but also imposes significant costs (20).

Most studies published during the past decade show an increasing focus on the use of palliative medicine as an accepted treatment in cancer patients, especially in patients who are in the last stages of their disease (6,19,35).

The present review study shows that most of these EE studies have been conducted in developed, high-income countries (e.g., UK, Canada, the US, Australia, Sweden, Belgium, Italy, The Netherlands, France, New Zealand, and Portugal) (20,32), which reveals a considerable gap in the literature from middle-income countries, as nearly 78% of those who require palliative care live in low- or middle-income nations.

The difference between the results of studies was due to the type of study, the time period when the costs and clinical outcomes were calculated, the differences in the disease groups and the type of cancer, the difference in the cost unit, the type of outcome effectiveness, and the perspectives of the studies.

A wide range of palliative medicine interventions was identified, including controlling and managing patients' pain through the use of analgesics, chemotherapy and radiotherapy, surgical procedures, home care, and hospital daycare (12). EE has also been selected for a wide range of cancers, that is, one type of cancer in some studies and more than one type of cancer in others. These two issues reduce the possibility of comparing different interventions. Although there are many differences in the type of cancer, the type of studies, and the characteristics of the studies, a consistent pattern is observed in the results of the studies. Palliative medicine was reported to be less expensive than the treatment group in most studies and this cost difference is statistically significant in most studies. The results of three studies also indicate that the use of palliative medicine compared to other conventional treatments not only has no survival benefit but also imposes significant costs (20).

Many of the reviewed studies were either based on the results of clinical trial studies or had a very small sample size. Regarding clinical trial studies, since the results cannot be easily generalized to other contexts, it is better to conduct a study in larger dimensions (23); because the study populations of the clinical trial studies were not large enough to make such comparisons. As a result, the results obtained in the comparison groups are not statistically significant or cause a high confidence interval. Therefore, it is necessary to conduct multi-center studies

with large sample sizes to investigate such methods as well as their potential sources and their outcomes.

In some studies, palliative care services are limited to outpatient or inpatient counseling, and in other studies, they include controlling and managing patients' pain through the use of analgesics, chemotherapy and radiotherapy, surgical procedures, home care, and hospital day-care. In most studies, costs are estimated only from the perspective of the service provider or payer (23,39). Future studies of palliative medicine should include a broader perspective on palliative care costs so that they take into account costs incurred by the patient, family, informal, and community care costs, such as out-of-pocket costs, opportunity costs, and travel costs. Regardless of all other costs mentioned above, the actual cost saving from palliative care programs may be underestimated.

Furthermore, various studies used different cost-effectiveness measurements. Because in many palliative care studies, the diversity of patients based on the type of cancer is very enormous, it is important to standardize outcomes to facilitate comparisons across different care.

Therefore, it can be stated that researchers should pay attention to the selection of effective measures and standardize these cases in order to generalize cost-effectiveness findings to the level of the health system. Besides, palliative care requires further agreement and homogeneity regarding standard measurements of resource use (such as nursing time, hospitalization, and acute care). Results of a recent study of different financing models in different countries show a very weak relationship between payments to palliative care providers and the needs of individuals, which in itself justifies and exacerbates unequal patterns in service delivery.

Considering that palliative medicine studies have been conducted very sparsely and in high-income countries, while applying their results, we should take into account items such as the incidence and prevalence and epidemiology of various types of cancer and treatments available in each country, in addition to considering the capital infrastructure, manpower, and existing capacities in the health system of that country. Conducting clinical trial studies and EE studies taking into account all the cases mentioned in the present study will be of great help to authorize to make the best use of this therapeutic approach in various cancers.

The main limitation of the present systematic study is the non-identification of all available evidence and literature related to palliative medicine. Considering the language constraint and the unavailability of the full-text articles, part of the studies will not be retrieved. Moreover, those studies that compared two or more palliative care services were excluded from the study. The main strengths of our study are adherence to the protocol and PRISMA principles, as well as reviewing the quality of current studies using the CHEERS checklist.

Conclusion

Although there are a wide variety of studies, characteristics, and quality of the final studies included in the present study, there are relatively favorable and stable pat-

terns regarding the results. Palliative care is usually less expensive than comparator groups, and the cost difference is statistically significant in most cases, and this treatment is a relatively cost-effective option. However, making the right relevant decision and applying it as a dominant therapy approach in different countries requires further study in larger populations and over a longer period.

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Conflict of Interests

The authors declare that they have no competing interests.

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