

# Integration of Early Specialist Palliative Care in Cancer Care and Patient Related Outcomes: A Critical Review of Evidence

Naveen Salins, Raghavendra Ramanjulu<sup>1</sup>, Lipika Patra<sup>2</sup>, Jayita Deodhar, Mary Ann Muckaden

Department of Palliative Medicine, Tata Memorial Centre, Mumbai, Maharashtra, <sup>1</sup>Integrative Oncology, HCG Bangalore Institute of Oncology, <sup>2</sup>Palliative Care Specialist, Karunashraya Hospice, Bengaluru, Karnataka, India

*Address for correspondence: Dr. Naveen Salins; E-mail: naveensalins@gmail.com*

## ABSTRACT

**Introduction:** World Health Organization and American Society of Clinical Oncology recommend early integration of specialist palliative care in patients with cancer. This paper focuses on critical review of evidence on integration of early specialist palliative care in cancer care and patient-related outcomes.

**Methods:** The question for the literature search was – Does integration of early specialist palliative care in cancer care influences patient-related outcomes? 31 articles related to literature search review question were included in this paper.

**Results:** Ten patient-related outcomes of early specialist palliative care in adult cancer care was studied. Studies by Temel *et al.* (2012), Bakitas *et al.* (2009), Zimmermann *et al.* (2014), Rugno *et al.* (2014), Lowery *et al.* (2013) and Walker *et al.* (2014) showed early specialist palliative care improves health-related quality of life (HRQOL). Studies by Piri *et al.* (2012), Lowery *et al.* (2013), and Walker *et al.* (2014) showed early specialist palliative care improved mood depression and anxiety. Studies by Zimmermann *et al.* and Rugno *et al.* (2014) showed symptom control benefit of early specialist palliative care. Studies by Temel (2010), Bakitas (2015) and Rugno *et al.* (2014) showed survival improvement with early specialist palliative care. All these studies were carried in ambulatory palliative care setting. No survival benefit of palliative care intervention was seen in inpatient palliative care setting. The studies by Geer *et al.* (2012), Rugno *et al.* (2014), and Lowery *et al.* (2013) showed that early palliative care intervention positively influences treatment decision making. All the studies showed that palliative care intervention group received less intravenous chemotherapy in last few weeks of life. Studies by Yoong *et al.* and Temel *et al.* (2011) shows early specialist palliative care improves advanced care planning. Studies by Temel *et al.* (2010), Greer *et al.* (2012), McNamara *et al.* (2013), Hui *et al.* (2014), and Kwon *et al.* (2013) showed that early specialist palliative care improves health care utilization, planned discharge, less emergency room visits, and better hospice utilization. Studies by Wiese *et al.* (2013), Hui *et al.* (2014) and Temel *et al.* (2010) showed that early specialist palliative care improves end-of-life care outcomes. Study by Rugno *et al.* (2014) showed that early specialist palliative care improves health-related communication. Studies by Wallen *et al.* (2012) and Zimmermann *et al.* (2014) shows early specialist palliative care improves patient and family satisfaction. There is a lack of robust evidence at present to support role of early specialist palliative care interventions in pediatric and geriatric oncology. Qualitative studies have demonstrated few negative outcomes of early specialist palliative care intervention.

**Conclusions:** In adult oncology, there is evidence to suggest early specialist palliative care improves HRQOL, mood, treatment decision-making, health care utilization, advanced care planning, patient satisfaction, and end-of-life care. There is moderate evidence to support the role of early specialist palliative care intervention in improvement of symptoms, survival, and health-related communication. There is limited evidence at present to support role of early specialist palliative care interventions in pediatric and geriatric oncology. Qualitative studies on barriers and negative patient outcomes may provide useful insights toward restructuring early specialist palliative care interventions.

**Key words:** Cancer, Early specialist palliative care, Patient-related outcomes

### Access this article online

#### Quick Response Code:



#### Website:

www.jpalliativecare.com

#### DOI:

10.4103/0973-1075.185028

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

**For reprints contact:** reprints@medknow.com

**How to cite this article:** Salins N, Ramanjulu R, Patra L, Deodhar J, Muckaden MA. Integration of early specialist palliative care in cancer care and patient related outcomes: A critical review of evidence. Indian J Palliat Care 2016;22:252-7.

## INTRODUCTION

The World Health Organization and American Society of Clinical Oncology have recommended early integration of specialist palliative care in patients with cancer.<sup>[1,2]</sup> The traditional models of palliative care delivery have expanded its scope to include newer models of care delivery such as integrated care model, shared care model, and pop-up model.<sup>[3]</sup> Early specialist palliative care delivery involves the integration of specialist palliative care early in the course of illness trajectory.<sup>[4]</sup> In recent times, early specialist palliative care has evolved itself as a novel model of palliative care delivery,<sup>[5]</sup> and there is gradual accumulation of evidence to support its role in cancer and noncancer setting.<sup>[6]</sup> This article would like to critically examine the evidence for and against integration of early specialist palliative care in cancer care with a specific focus on patient related outcomes.

## METHODS

The question for the literature search was – Does integration of early specialist palliative care in cancer care influences patient-related outcomes? The search was carried out using electronic databases such as MEDLINE, CINAHL, PsycINFO, PubMed, Scopus, and Web of Science. The Boolean operators used for literature search was early or timing AND specialist palliative care AND cancer or oncology AND patient-related outcomes. To answer the literature search question, randomized controlled trials (RCTs), systematic review, surveys, observational studies, and qualitative studies were included. Opinion papers, editorials, and letters to editors were excluded. Only those papers related to early specialist palliative care in cancer care was included and other research relating to nonspecialist and nonearly palliative care intervention was excluded. Only research published in English language in the last 10 years (2005 and later) were included. All unpublished literature and grey literature were excluded. About 31 research papers were included in the final review. Each research paper was analyzed, and outcomes were presented along with reviewer's own discussion of results.

## RESULTS OF REVIEW

### Early specialist palliative care and patient-related outcomes in adult oncology

#### *Health-related quality of life*

According to studies, early specialist palliative care improves health-related quality of life (HRQOL).<sup>[7-12]</sup>

The study by Temel *et al.*<sup>[7]</sup> in nonsmall cell lung cancer (NSCLC) was an adequately powered RCT to detect HRQOL improvement. However, actual difference in mean HRQOL scores between standard oncology group and specialist palliative care group was marginal. It is not clear whether such small changes in the score could confer clinical benefit. RCT by Bakitas *et al.*<sup>[8]</sup> (ENABLE II trial) focused on patient empowerment through specialist nurse led education and telehealth in a mixed group of cancer population. This was an adequately powered RCT and HRQOL tools used met the minimally clinically important difference (MCID) and standard deviation criteria. However, a follow-up RCT, i.e. ENABLE III Trial<sup>[13]</sup> failed to demonstrate improvement in HRQOL. ENABLE III trial compared the effect of 3-month early and delayed specialist palliative care intervention on HRQOL. Three months may be too short to appreciate HRQOL benefits of specialist palliative care in a mixed group of cancer, as the illness trajectories and baseline symptom/HRQOL scores differ between malignancies. A similar RCT, focusing on nurse led education intervention showed improvement in HRQOL.<sup>[14]</sup> However, this RCT was terminated prematurely, and the study was grossly underpowered. A cluster RCT in a mixed cancer population by Zimmermann *et al.*<sup>[9]</sup> showed statistically significant improvement in HRQOL scores at 4-month end point. This trial was primarily designed to assess the improvement in HRQOL at 3 months. RCTs in palliative care research measuring the delayed outcomes of an intervention, may have limitations and observational studies may be useful.<sup>[15]</sup> Although specialist palliative care interventions in Temel *et al.* and Zimmermann *et al.* were similar, the delay in HRQOL improvement may be due to different group of population studied. RCT by Rugno *et al.*<sup>[11]</sup> in advanced gynec-oncology patients showed significant improvement in HRQOL. This RCT had a selection bias due to the lack of palliative care referral protocol. The RCTs by Walker *et al.*<sup>[10]</sup> and Lowery *et al.*<sup>[12]</sup> were primarily designed to assess the improvement in depression and cost benefit, respectively. HRQOL was a secondary endpoint. While few other RCTs<sup>[16-18]</sup> have demonstrated HRQOL benefits of palliative care, these interventions were either not specialist palliative care or was not initiated early in the course of illness.

#### *Mood, depression, and anxiety*

According to studies, early specialist palliative care improves mood, depression, and anxiety.<sup>[10,11,19]</sup> RCTs by Pirl *et al.*<sup>[19]</sup> and Walker *et al.*<sup>[10]</sup> showed that improvement in depression was independent of pharmacological treatment. In the study by Pirl *et al.*, improvement in depression scores did not correlate with improved survival. A possible explanation could be that epidermal growth factor receptor

wild type mutation in lung cancer is an independent risk factor influencing depression and survival.<sup>[20]</sup> In RCTs by Pirl *et al.* and Walker *et al.*, patients in both groups received antidepressants. Improvement in depression may be due to intense counseling, phone follow-up, and regular titration of antidepressants in the specialist palliative care intervention group. Two RCTs by Bakitas *et al.* (ENABLE II and III trials) showed no improvement in anxiety and depression with specialist palliative care intervention.<sup>[8,13]</sup> This may be due to the specialist palliative care intervention in these trials being mainly psycho-education with limited clinical input from specialist palliative care physicians. ENABLE III trial was not adequately powered to detect patient-reported outcomes.

### *Symptom control*

According to studies, early specialist palliative care intervention improves symptoms<sup>[9,11,21]</sup> The RCT by Zimmermann *et al.*<sup>[9]</sup> showed symptom improvement at 4 months. Here, the trial was originally designed to detect symptom improvement at 3 months. Furthermore, in this study, the actual difference in symptom scores was marginal. This may be due to low symptom burden in early specialist palliative care group. This is evident as many study subjects declined to participate in the study during screening due to the lack of symptoms. The RCT by Rugno *et al.*<sup>[11]</sup> showed only improvement in insomnia. The retrospective review of medical records by Kwon *et al.*,<sup>[21]</sup> had both selection bias and referral bias. This study had no protocol for palliative care referral, and palliative outpatient services was called supportive care services to source more referral. Two RCTs, ENABLE II<sup>[8]</sup> and ENABLE III<sup>[13]</sup> did not show any improvement in symptoms. This could be because specialist palliative care interventions were nurse led education interventions with limited specialist palliative care physician input. A mixed method (RCT and qualitative) study in surgical oncology patients showed no perceived improvement in symptoms with early specialist palliative care intervention.<sup>[22]</sup> However, the patients in the study group felt reassured knowing pain and palliative care services were available. This study was underpowered to detect MCID difference for pain, and the patients had a combination of postoperative and cancer pain.

### *Survival*

According to studies, early specialist palliative care improves survival.<sup>[7,8,11,13]</sup> RCTs by Temel *et al.*<sup>[7]</sup> and Bakitas *et al.*<sup>[13]</sup> were conducted in outpatient ambulatory setting. However, RCTs studying hospital- and home-based palliative care model did not show survival improvement with palliative care intervention.<sup>[23,24]</sup> In the study by Temel *et al.*, survival

benefit was not the study end point, and it was achieved following several secondary *post hoc* analyses. The trial was underpowered to show survival benefit. Cancer staging, extent of chemotherapy received, and baseline comorbid illness were not clearly stated. These could be confounding factors when estimating survival benefit. Although in the study by Bakitas *et al.*, the survival benefit was not statistically significant, 15% improvement in median survival is clinically significant. The studies by Brumley *et al.*<sup>[24]</sup> and Gade *et al.*<sup>[23]</sup> studying home- and hospital-based palliative care models, had a heterogeneous population of cancer and noncancer with multiple comorbid conditions and poor performance status. Although these patient population groups did not have survival benefit, they had good relief of symptoms, emotional well-being, and satisfaction of care. Hence, survival benefit may not be a reliable marker of specialist palliative care intervention in these settings. RCT by Rugno *et al.*<sup>[11]</sup> has correlated survival benefit to improved HRQOL. This view is supported by other RCTs.<sup>[7,13]</sup> There is conflicting evidence on the improvement in depression correlating with improved survival.<sup>[13,19]</sup> A positive correlation is seen between receiving less intravenous (IV) chemotherapy, and early hospice referral with improved survival.<sup>[11,25]</sup>

### *Treatment decision making*

A RCT in NSCLC<sup>[25]</sup> showed that early specialist palliative care intervention decreased use of IV chemotherapy in the last 2 months of life, and there was longer time gap between IV chemotherapy and death. Survival was longer in the group with less IV chemotherapy. This could be due to <10% response to second line IV chemotherapy, significant side effects of IV chemotherapy causing inadvertent shortening of life<sup>[26]</sup> and greater efficacy of oral chemotherapy<sup>[27]</sup> in advanced NSCLC. Timely cessation of chemotherapy at the end-of-life also facilitates early hospice referral.<sup>[28,29]</sup> In the study by Greer *et al.*,<sup>[25]</sup> chemotherapy decision-making was not envisaged as the study outcome during trial design and chemotherapy regimens between the groups were not standardized. The study was carried out in NSCLC patients and results of this study cannot be extrapolated to other malignancies such as breast or head and neck cancers with a more indolent course. Findings of RCT by Geer *et al.*<sup>[25]</sup> are supported by studies in advanced gynec-oncology patients<sup>[11]</sup> and advanced ovarian cancer patients,<sup>[12]</sup> which has also shown less chemotherapy use in last months of life.

### *Advanced care planning*

According to studies, early specialist palliative care improves illness perception, goals of care discussion, and

advanced care planning.<sup>[30,31]</sup> In the RCT by Temel *et al.*<sup>[30]</sup> in NSCLC patients receiving early specialist palliative care intervention, higher proportion of patients were aware that their disease was not curable at 12 weeks. Furthermore, the patients in early palliative care group had better awareness that the goal of cancer treatment was not cure. Patients who had better illness perception and better awareness of goals of treatment received less IV chemotherapy at end-of-life. Although this study was adequately powered, it did not use a validated tool to assess illness perception. The study findings were supported by a qualitative study by Yoong *et al.*<sup>[31]</sup> However, this qualitative study was a retrospective analysis of medical records.

#### *Health-resource utilization and health-related cost*

According to studies, early specialist palliative care decreases acute hospital admission, emergency department visits, and length of hospital stay. It promotes early hospice referral and increases duration of hospice stay.<sup>[7,12,21,25,32,33]</sup> However, results of ENABLE II<sup>[8]</sup> and ENABLE III<sup>[13]</sup> trials failed to show health resource utilization benefits. Studies by Temel *et al.*<sup>[7]</sup> and Greer *et al.*<sup>[25]</sup> were adequately powered RCTs conducted in ambulatory NSCLC setting. Study by Lowery *et al.*<sup>[12]</sup> studied cost saving benefit and health care utilization in platinum resistant ovarian cancer, which has similar prognostic outcomes as NSCLC. All these three studies were conducted at the USA and early hospice referral was attributed to receiving less IV chemotherapy at the end-of-life. The study findings are relevant for the United States setting, as patients cannot access concurrent hospice care alongside IV chemotherapy.<sup>[29]</sup> Studies by McNamara *et al.*,<sup>[32]</sup> Hui *et al.*,<sup>[33]</sup> and Kwon *et al.*<sup>[21]</sup> were retrospective study of medical records and in all these studies, the data were not primarily collected for research purposes. A pilot-RCT on role of advanced registered nurse practitioner discussing benefits of hospice showed nonsignificant improvement in hospice knowledge and hospice referral.<sup>[14]</sup> This RCT was grossly underpowered to detect such improvement.

Early specialist palliative care is associated with reduced healthcare-related costs.<sup>[12,34,35]</sup> The review by Smith *et al.*<sup>[34]</sup> had a mixture of RCTs, non-RCTs, cohort, and case-controlled studies that demonstrated cost saving benefit of palliative care. However, majority of studies in this review were non-RCTs, from United States, and emphasized direct cost benefits. Studies by May *et al.*<sup>[35]</sup> and Lowery *et al.*<sup>[12]</sup> were cohort studies and had selection biases due to selective palliative care referral.

#### *End-of-life care*

According to studies, early specialist palliative care improves the end-of-life care outcomes.<sup>[7,33,36]</sup> In the RCT by Temel

*et al.*,<sup>[7]</sup> the early specialist palliative care group received less aggressive medical interventions at the end-of-life and higher rates of documentation of end-of-life preferences. These findings were supported by studies by Hui *et al.*<sup>[33]</sup> and Wiese *et al.*<sup>[36]</sup> This could be due to the fact that earlier palliative care referral in outpatient setting provides room for longer therapeutic relationship, discussion of goals of care, and advanced care planning, which could facilitate improved end-of-life care outcomes. The study by Hui *et al.* was a retrospective cohort study, and study by Wiese *et al.* was a prospective survey of palliative care experts and emergency medicine physicians.

#### *Health-related communication*

According to a RCT, early specialist palliative care improves health-related communication.<sup>[11]</sup> Study by Rugno *et al.*<sup>[11]</sup> did not use standardized tool for communication assessment. RCT by Zimmermann *et al.*<sup>[9]</sup> in a mixed cancer population did not show health-related communication benefits of early specialist palliative care.<sup>[9]</sup> According to the authors, lack of improvement could be possibly due to a negatively worded clinician communication assessment scale.

#### *Patients and family satisfaction of care*

According to studies, early specialist palliative care improves patient and family satisfaction of care.<sup>[9,22]</sup> A mixed method study (RCT and qualitative) by Wallen *et al.*<sup>[22]</sup> in surgical oncology patients showed presence of palliative care team, reassured the patients, and patients identified palliative care providers as patient advocates. This RCT was not adequately powered and crossover between the arms was permitted at clinician's discretion. Satisfaction of care in the RCT by Zimmermann *et al.*<sup>[9]</sup> was measured with a standard validated tool, and the results were statistically significant.

#### **Early specialist palliative care and patient outcomes in pediatric and geriatric oncology**

A prospective longitudinal cohort study in children with cancer and noncancer needing stem cell transplantation showed symptom control benefit with early specialist palliative care intervention.<sup>[37]</sup> This was a feasibility study involving small patient sample and specific symptom improvement was not assessed. A retrospective chart review in standard risk medulloblastoma showed HRQOL improvement and less chemotherapy side effects with early specialist palliative care intervention.<sup>[38]</sup> In this study, early specialist palliative care intervention was defined as administering IV chemotherapy and IV fluids at home. However, this is not routinely considered as a standard palliative care intervention. The study was a retrospective chart review with no comparator group.

In the elderly population, a retrospective chart review had shown early specialist palliative care intervention was found to be associated with lower length of hospital stay, less hospital deaths, and more hospice deaths.<sup>[39]</sup> In this study, the data used were not collected for research, and there was no clear documentation of cancer staging.

### Early specialist palliative care referral and negative patient outcomes

Qualitative studies interviewing clinicians and healthcare providers have described few negative patient outcomes of early specialist palliative care referral.<sup>[40-42]</sup> According to these studies, palliative care clinicians may not have the skills and competence to appreciate benefits of disease modifying therapies and may be unable to identify potentially reversible disease-related complications. There could be breaks in coordination of care with clinicians not clear of their roles and responsibilities and patients confused about the suitable specialty consultation in a given clinical situation. There could be communication gaps with patients and caregivers receiving mixed messages from oncologists and palliative care providers. There might be ethical dilemmas in timing of palliative care referral in clinical situations with unclear illness trajectory and uncertain prognosis. Dealing with patient's unrealistic expectation and dealing with patient's perceptions of palliative care referral could be challenging for the oncologists. Logistics involved in palliative care referral, timely access, and additional costs involved could be other barriers for palliative care referral. All these qualitative studies had disproportionately higher number of physicians with a small group of other health care providers.

### CONCLUSIONS

Role of early specialist palliative care and patient outcomes in adult oncology have been extensively studied. There is a paucity of literature on role of early specialist palliative care intervention in pediatric and geriatric oncology. In adult oncology, there is evidence to suggest early specialist palliative care improves HRQOL, mood, treatment decision-making, healthcare utilization, advanced care planning, patient satisfaction, and end-of-life care. However, there is moderate evidence to support role of early specialist palliative care intervention in improvement of symptoms, survival and health related communication. There is limited evidence to support role of early specialist palliative care interventions in pediatric and geriatric oncology. Qualitative studies on barriers and negative patient outcomes may provide useful insights toward

restructuring early specialist palliative care interventions. Further research and build-up of evidence is needed to facilitate development of early specialist care intervention as one more model of palliative care delivery.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

### REFERENCES

1. WHO. WHO Definition of Palliative Care; 2013. Available from: <http://www.who.int/cancer/palliative/definition/en/>. [Last accessed on 2013 Nov 13].
2. Smith TJ, Temin S, Alesi ER, Abernethy AP, Balboni TA, Basch EM, *et al.* American Society of Clinical Oncology provisional clinical opinion: The integration of palliative care into standard oncology care. *J Clin Oncol* 2012;30:880-7.
3. Lockett T, Phillips J, Agar M, Virdun C, Green A, Davidson PM. Elements of effective palliative care models: A rapid review. *BMC Health Serv Res* 2014;14:136.
4. Dalgaard KM, Bergholtz H, Nielsen ME, Timm H. Early integration of palliative care in hospitals: A systematic review on methods, barriers, and outcome. *Palliat Support Care* 2014;12:495-513.
5. Hannon B, Swami N, Pope A, Rodin G, Dougherty E, Mak E, *et al.* The oncology palliative care clinic at the Princess Margaret Cancer Centre: An early intervention model for patients with advanced cancer. *Support Care Cancer* 2015;23:1073-80.
6. Howie L, Peppercorn J. Early palliative care in cancer treatment: Rationale, evidence and clinical implications. *Ther Adv Med Oncol* 2013;5:318-23.
7. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, *et al.* Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010;363:733-42.
8. Bakitas M, Lyons KD, Hegel MT, Balan S, Brokaw FC, Seville J, *et al.* The project ENABLE II randomized controlled trial to improve palliative care for patients with advanced cancer. *JAMA* 2009;302:741-9.
9. Zimmermann C, Swami N, Krzyzanowska M, Hannon B, Leigh N, Oza A, *et al.* Early palliative care for patients with advanced cancer: A cluster-randomised controlled trial. *Lancet* 2014;383:1721-30.
10. Walker J, Hansen CH, Martin P, Symeonides S, Gourley C, Wall L, *et al.* Integrated collaborative care for major depression comorbid with a poor prognosis cancer (SMaRT Oncology-3): A multicentre randomised controlled trial in patients with lung cancer. *Lancet Oncol* 2014;15:1168-76.
11. Rugno FC, Paiva BS, Paiva CE. Early integration of palliative care facilitates the discontinuation of anticancer treatment in women with advanced breast or gynecologic cancers. *Gynecol Oncol* 2014;135:249-54.
12. Lowery WJ, Lowery AW, Barnett JC, Lopez-Acevedo M, Lee PS, Secord AA, *et al.* Cost-effectiveness of early palliative care intervention in recurrent platinum-resistant ovarian cancer. *Gynecol Oncol* 2013;130:426-30.
13. Bakitas MA, Tosteson TD, Li Z, Lyons KD, Hull JG, Li Z, *et al.* Early versus delayed initiation of concurrent palliative oncology care: Patient outcomes in the ENABLE III randomized controlled trial. *J Clin Oncol* 2015;33:1438-45.
14. Dyar S, Lesperance M, Shannon R, Sloan J, Colon-Otero G. A nurse practitioner directed intervention improves the quality of life of patients with metastatic cancer: Results of a randomized pilot study. *J Palliat Med* 2012;15:890-5.
15. Rothwell PM, Bhatia M. Reporting of observational studies. *BMJ* 2007;335:783-4.
16. McMillan SC, Small BJ, Weitzner M, Schonwetter R, Tittle M, Moody L,

- et al.* Impact of coping skills intervention with family caregivers of hospice patients with cancer: A randomized clinical trial. *Cancer* 2006;106:214-22.
17. Rummans TA, Clark MM, Sloan JA, Frost MH, Bostwick JM, Atherton PJ, *et al.* Impacting quality of life for patients with advanced cancer with a structured multidisciplinary intervention: A randomized controlled trial. *J Clin Oncol* 2006;24:635-42.
  18. Moore S, Corner J, Haviland J, Wells M, Salmon E, Normand C, *et al.* Nurse led follow up and conventional medical follow up in management of patients with lung cancer: Randomised trial. *BMJ* 2002;325:1145.
  19. Pirl WF, Greer JA, Traeger L, Jackson V, Lennes IT, Gallagher ER, *et al.* Depression and survival in metastatic non-small-cell lung cancer: Effects of early palliative care. *J Clin Oncol* 2012;30:1310-5.
  20. Pirl WF, Traeger L, Greer JA, Bemis H, Gallagher E, Lennes I, *et al.* Tumor epidermal growth factor receptor genotype and depression in stage IV non-small cell lung cancer. *Oncologist* 2011;16:1299-306.
  21. Kwon JH, Hui D, Chisholm G, Ha C, Yennurajalingam S, Kang JH, *et al.* Clinical characteristics of cancer patients referred early to supportive and palliative care. *J Palliat Med* 2013;16:148-55.
  22. Wallen GR, Baker K, Stolar M, Miller-Davis C, Ames N, Yates J, *et al.* Palliative care outcomes in surgical oncology patients with advanced malignancies: A mixed methods approach. *Qual Life Res* 2012;21:405-15.
  23. Gade G, Venohr I, Conner D, McGrady K, Beane J, Richardson RH, *et al.* Impact of an inpatient palliative care team: A randomized control trial. *J Palliat Med* 2008;11:180-90.
  24. Brumley R, Enguidanos S, Jamison P, Seitz R, Morgenstern N, Saito S, *et al.* Increased satisfaction with care and lower costs: Results of a randomized trial of in-home palliative care. *J Am Geriatr Soc* 2007;55:993-1000.
  25. Greer JA, Pirl WF, Jackson VA, Muzikansky A, Lennes IT, Heist RS, *et al.* Effect of early palliative care on chemotherapy use and end-of-life care in patients with metastatic non-small-cell lung cancer. *J Clin Oncol* 2012;30:394-400.
  26. Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, *et al.* Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004;22:1589-97.
  27. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, *et al.* Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123-32.
  28. Christakis NA, Escarce JJ. Survival of medicare patients after enrollment in hospice programs. *N Engl J Med* 1996;335:172-8.
  29. Casarett D, Johnson M, Smith D, Richardson D. The optimal delivery of palliative care: A national comparison of the outcomes of consultation teams vs inpatient units. *Arch Intern Med* 2011;171:649-55.
  30. Temel JS, Greer JA, Admane S, Gallagher ER, Jackson VA, Lynch TJ, *et al.* Longitudinal perceptions of prognosis and goals of therapy in patients with metastatic non-small-cell lung cancer: Results of a randomized study of early palliative care. *J Clin Oncol* 2011;29:2319-26.
  31. Yoong J, Park ER, Greer JA, Jackson VA, Gallagher ER, Pirl WF, *et al.* Early palliative care in advanced lung cancer: A qualitative study. *JAMA Intern Med* 2013;173:283-90.
  32. McNamara BA, Rosenwax LK, Murray K, Currow DC. Early admission to community-based palliative care reduces use of emergency departments in the ninety days before death. *J Palliat Med* 2013;16:774-9.
  33. Hui D, Kim SH, Roquemore J, Dev R, Chisholm G, Bruera E. Impact of timing and setting of palliative care referral on quality of end-of-life care in cancer patients. *Cancer* 2014;120:1743-9.
  34. Smith S, Brick A, O'Hara S, Normand C. Evidence on the cost and cost-effectiveness of palliative care: A literature review. *Palliat Med* 2014;28:130-50.
  35. May P, Garrido MM, Cassel JB, Kelley AS, Meier DE, Normand C, *et al.* Prospective cohort study of hospital palliative care teams for inpatients with advanced cancer: Earlier consultation is associated with larger cost-saving effect. *J Clin Oncol* 2015;33:2745-52.
  36. Wiese CH, Lassen CL, Bartels UE, Taghavi M, Elhabash S, Graf BM, *et al.* International recommendations for outpatient palliative care and prehospital palliative emergencies – A prospective questionnaire-based investigation. *BMC Palliat Care* 2013;12:10.
  37. Lafond DA, Kelly KP, Hinds PS, Sill A, Michael M. Establishing feasibility of early palliative care consultation in pediatric hematopoietic stem cell transplantation. *J Pediatr Oncol Nurs* 2015;32:265-77.
  38. Madden JR, Vaughn EA, Northouse B, Tong S, Dorneman LA, Foreman NK, *et al.* Benefits of using an early palliative care intervention in pediatric oncology: Quality of life and cost savings related to home delivery of cisplatin. *J Hosp Palliat Nurs* 2015;17:319-24.
  39. Reyes-Ortiz CA, Williams C, Westphal C. Comparison of early versus late palliative care consultation in end-of-life care for the hospitalized frail elderly patients. *Am J Hosp Palliat Care* 2015;32:516-20.
  40. Le BH, Mileskin L, Doan K, Seward D, Spruyt O, Yoong J, *et al.* Acceptability of early integration of palliative care in patients with incurable lung cancer. *J Palliat Med* 2014;17:553-8.
  41. Pfeil TA, Laryionava K, Reiter-Theil S, Hiddemann W, Winkler EC. What keeps oncologists from addressing palliative care early on with incurable cancer patients? An active stance seems key. *Oncologist* 2015;20:56-61.
  42. Dalberg T, Jacob-Files E, Carney PA, Meyrowitz J, Fromme EK, Thomas G. Pediatric oncology providers' perceptions of barriers and facilitators to early integration of pediatric palliative care. *Pediatr Blood Cancer* 2013;60:1875-81.