Review Article

A review of the trials which examine early integration of outpatient and home palliative care for patients with serious illnesses

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Background: Palliative care has emerged as care that specifically aims to address gaps inherent in disease-centered approaches in order to enhance care quality in serious illness, both for patients and families and for health care systems. Late palliative care for patients with serious illness mitigates benefits to patients, families, and health care systems. Efforts have been made by investigators to define the impact of earlier palliative care interventions on patient, family and health care systems outcomes. We conducted a systematic review of randomized trials of outpatient and home palliative care, two locations where earlier palliative care do occur, to examine the evidence for palliative care benefits.

Methods: Various terms were used; the search was performed in PubMed. From this search randomized trials were selected from 62 references derive from this search which appeared to be primary studies. Hand searches were done on references. Fifteen randomized control trials of outpatient palliative care and 13 randomized control trials of palliative home care were collected and collated into tables. Seven systematic reviews obtained and outcomes summarized in a table.

Results: Advantages to palliative care include improvement in certain symptoms such as depression, improved patient quality of life, reduced aggressive care at the end of life, increased advanced directives, reduced hospital length of stay and hospitalizations, improved caregiver burden and better maintenance of caregiver quality of life and reduction in the medical cost of care as well as patient and family satisfaction. There are randomized trials which demonstrate that symptoms and quality of life are not improved, and resource utilization and costs are not different from "usual" care. Seven systematic reviews of randomized trials came to similar conclusions.

Discussion: Notable methodological issues account for differences in results. Definitions of "early" palliative care vastly differed. There were no descriptions of what was meant by "usual" care in the control arm. Study designs and procedures were frequently flawed. Populations were heterogeneous in many studies and imbalances between randomly-allocated occurred frequently. Direct patient care versus consultation only, played a role. The assumption that the same model of care was equally effective across different diseases was unsubstantiated. Attrition was on average 40% and blinding of individuals who assessed outcomes frequently not mentioned. Power calculations were infrequent. Intention to treat analysis was often not done. Current studies fell short of the goal of measuring all relevant factors to assessing costs-benefits, having largely ignored the cost to the patient and family and instead focused narrowly on patient medical costs.

Conclusions: Multiple studies have demonstrated several benefits to early outpatient palliative care for patients with newly diagnosed metastatic cancer. However, better designed and executed studies are needed to determine the best time to intervene and the best model of care.

Keywords: Palliative; early; outpatient; home; outcomes

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Introduction and definitions

The disease-centered, pathophysiological approach to medical care and the development of targeted innovations to various disease processes has brought about notable improvements in the technical aspects of managing disease. However, though the reductionist approach has brought about many advances, the sum of the advances is often less than the quality of care that is desired (1,2). The result is a dramatic increase in health care costs relative to outcomes. For example, in the United States rapidly rising health care costs have not lead to commensurate improvements in quality of health care compared to other economically developed countries (3). Technical advancements in care have not fully translated into benefits in quality of care at least in part due to the fact that the disease-centered approach often neglects the multi-dimensional aspects of patient and family quality of life, including physical and psychosocial-spiritual aspects of wellbeing. This gap is most apparent in the context of chronic and serious illnesses, where technological advancement and attendant costs are escalating rapidly; patient and family suffering is often multidimensional and significant; and care communication and decision-making is highly complex and enmeshed with values and goals.

Palliative care has emerged as an approach to care that specifically aims to address this gap inherent to the disease-centered approach in order to enhance care quality in the setting of serious illness, both for patients and their families and for health care systems. According to the World Health Organization's definition, palliative care is an approach to care that aims to "improve the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual" (http://www.who.int/cancer/palliative/definition/en/). Palliative care is an approach to care that is applicable across the serious illness trajectory, from diagnosis to death, and hence aims to be practiced in concert with technical aspects of disease-focused care. However, despite this aim, palliative care is frequently involved in patient/family care late in the course of a serious illness (4-7). This late application of palliative care to patients with serious illness is thought to mitigate its potential benefits to patients, their families, and health care systems. Hence, efforts have been made by investigators to define the impact of earlier palliative care interventions within the context of serious illnesses, including patient, family and health care systems outcomes.

Table 1 Themes of the review

Definitions of early palliative care
Advantage to early integration of palliative care
Differences in outcomes between randomized trials
The economics of palliative care
Models of palliative care
Future directions in research

The purpose of this article is to review and discuss randomized control trials examining the integration of palliative care earlier in the course of the disease trajectory for patients with serious illnesses as an outpatient and at home. The themes that this review will cover are listed on *Table 1*. In the outpatient clinic and at home are more likely to be locations where patients with life-limiting illnesses are likely to be seen early in the course of their disease. In addition, this article will summarize systematic reviews of palliative care and its impact on quality of care outcomes. Finally, the review will, in addition to reviewing the outcomes of these trials, discuss their methodological differences, strengths, and weaknesses, and with this backdrop explore how these may contribute to heterogeneity of findings.

Methods

A systematic review of palliative care randomized control trials was performed. Various terms were used and the search was performed in PubMed. Search terms and yields were: "Therapy-Broad AND early palliative care cancer" (846 references), "systematic AND early palliative care cancer" (102 references), "early palliative care and quality of care" (702 references), "early palliative care and economics" (112 references), "early palliative care and outcomes" (325 references), "early palliative care and hospice" (187 references), "early palliative care and aggressive care" (166 references), "early palliative care and benefits" (120 references). From this search randomized trials were selected from 62 references derive from this search which appeared to be the primary studies. Hand searches were done on these references. Fifteen randomized control trials of outpatient palliative care and 13 randomized control trials of palliative home care were collected and collated into tables (*Tables 2,3*). Three of the manuscripts were reports

Table 2 Randomized trials of outpatient palliative care

Reference	Patient	Intervention	Controls	Outcome measures	Results	Comments
Temel *et al.* (8) [2010]	Advanced non-small cell lung cancer—newly diagnosed	• Palliative care—physician/nurse specialist • Guidelines—National Consensus Project for Quality Palliative Care	"Usual care"	• FACT-L-QoL • HADS—anxiety depression • Aggressive care at the end of life—12 weeks • PHQ-9	• ↑ QoL difference TOI 6.0 • ↓ Aggressive care at end of life 33% *vs.* 54% • ↑ Advanced directive preference • ↑ Duration of hospice 11 *vs.* 4 days • Improved survival 11.6 *vs.* 8.9 months	• No to little attrition meaningful change in outcome measures • Positive primary and secondary outcomes
Greer *et al.* (9) [2012]* additional outcomes from Temel *et al.* (8) [2010]	Advanced non-small cell lung cancer	• Palliative care—physician/nurse specialist • Guidelines—National Consensus Project for Quality Palliative Care (8)	"Usual care"	• First and total chemotherapy • Hospice enrollment	• No different in chemotherapy lines • Chemotherapy within 60 days 57.5% *vs.* 70% (or 0.47) • Decrease IV chemotherapy at end of life • Hospice >7 days, 60% *vs.* 33%	• As above
Pirl *et al.* (10) [2012]* additional outcomes from Temel *et al.* (8) [2010]	Advanced non-small cell lung cancer	• Palliative care (8)	"Usual care"	• PHQ-9 • Depression	• Reduced depression 43% *vs.* 0% • Depression predicted reduced survival 5.4 *vs.* 10 months	• As above
Clark *et al.* (11) [2006]	Patients with cancer undergoing radiation plus caregivers >6 months life expectancy	• Exercise cognitive behavior therapy • Discussion • Support • Eight sessions, 90 minutes	Standard radiation oncology care	• Linear analog self-assessment—QoL • Burden interview—caregiver responsibility	• No improved QoL • No reduction in caregiver burden	• Underpowered for outcomes

Table 2 (*continued*)

Table 2 *(continued)*

Reference	Patient	Intervention	Controls	Outcome measures	Results	Comments
Aiken *et al.* (12) [2006]	Advanced COPD and heart failure	• Registered nurse manager—care coordinator • Symptom assessment • Continuity • Education	Usual care under managed care organization	• Memorial symptom assessment scale • SF-36/health survey • Service utilization	• Advanced directives 71% *vs.* 68% • Lower symptom distress for heart failure not COPD • Improved physical function at 9 months • No change in individual symptoms • No change in resource utilization	• Imbalances • Change in managed care during study • Attrition • Not an intention to treat analysis
Miller *et al.* (13) [2005]	Multiple diseases life expectancy >6 months + caregivers	• Adult affective education and support • Monthly meetings > minutes	Usual care	• Beck Depression Inventory • Spielberger State Anxiety Inventory • Spiritual Well-Being Scale • Death Distress Scale • Illness Disability Index	• No improvement in depression, anxiety, spirituality, death, meaninglessness improved	• Attrition • Not an intention to treat analysis • No power calculations • Outcomes were multiple for number analyzed
Raftery *et al.* (14) [1996]	Advanced cancer patients <1 year expected survival (85%)	• Nurse specialist—coordination of care	Usual care	• Costs—direct and indirect • Inpatient events • Outpatient events • Specialty appointments • Home visits • Social services • Mortality	• Survival unchanged • Fewer hospital days • Fewer admissions (2.5 *vs.* 3.3) • More outpatient visits (18 *vs.* 10.1) • Mean cost of intervention 4733 L (SD 8721) *vs.* 8034 L (SD 8721) • Most health care cost inpatient (75%)	• Not intention to treat analysis • Skewed population • Costs expressed in mean with wide standard deviation skewed
Bakitas *et al.* (15) [2009]	Newly diagnosed cancer patients (advanced cancer)	• Four instruction sessions • Monthly phone calls until death	Usual care	• FACT-QoL • ESAS—symptoms • CES-D—mood • Advanced directives • Chemotherapy • ED visits • Radiation	• No differenc in chemotherapy, hospital days, ICU stays, advanced directive, radiation or symptoms • Lower depression (–1.8) (SD 0.81) • Improved QoL 4.6 (SD)	• No change in resource utilization

Table 2 *(continued)*

Table 2 *(continued)*

Reference	Patient	Intervention	Controls	Outcome measures	Results	Comments
Addington-Hall *et al.* (16) [1992]	Advanced cancer patients	• Coordinated care by advanced practice nurse	Usual care	• HADS-depression, anxiety symptoms • Family Apgar Scale • Spritzer QoL Index • Caregiver—Leed's Depression Anxiety Scale	• No difference in needs for impaired ADL • No difference family finances (38% spent savings) • No difference in symptoms • Few differences ½ carers had to take time off	• Imbalances—borderline reduction in survival in controls (P=0.06)
Engelhardt *et al.* (17) [2006]	COPD; heart failure; cancer (advanced)	• Advanced illness coordinated care program • Physician support • Health literacy • Care coordination • Psychosocial care • Advanced care planning • Emotional support • Six teaching sessions	Usual care	• Satisfaction • Effectiveness of patient-provider communication • Surrogate experience • End of life family interview questionnaires • Costs	• Satisfaction increased • No difference in attitude of participation • Surrogate satisfaction not different • Mean cost of intervention $12,123 (SD 16,036) • Cost of usual care $16,295 (SD 28,491) • Advanced directive increased with intervention	• Effect size of satisfaction 0.18 • Effect size cost 0.18 • Non-validated scale • Skewed outcomes • Cross comparison done rather than mean changes • Economic accounting may be charges rather than costs • Economic outcomes did not include family costs, lost work, absenteeism • No power calculations • Heterogeneous population
McMillan and Small (18) [2007]	Hospice patients plus surrogate—3 groups	• COPE intervention • Dyspnea • Pain • Constipation • Problem-solving education	Usual care	• Pain by NRS • Dyspnea intensity scale • Memorial symptom assessment scale • Hospice QoL Index	• Only Memorial Symptom Assessment Scale improved 2.5-4 points	
McMillan *et al.* (19) [2006]	Hospice patients plus caregiver	• COPE problem-solving intervention	Usual care	• Caregiver QoL memorial assessment scale • General self-mastery questionnaire • Caregiver demand scale secondary outcome • Brief COPE scale • Short portable mental status scale	• Improved QoL 0.16 (SE 0.07) • Improved symptom burden—0.14 (SE 0.04) • Improved caregiver task burden 0.01 (SE 0.01)	• Underpowered 480 dyads; 329 randomized 60-70% attrition day 30 • Multiple outcomes corrected? • Assessors not mentioned • SE instead of SD

Table 2 *(continued)*

Table 2 *(continued)*

Reference	Patient	Intervention	Controls	Outcome measures	Results	Comments
Rabow *et al.* (20) [2004]	Cancer; COPD; heart failure; survival 1-5 years	• 1 year outpatient palliative care team—monthly discussion on symptoms, advanced directives, medical pharmacy, student support, weekly calls	Usual care	• Rapid Disability Rating Scale • Profile in mood state—depression spiritual well-being scale • Multi-dimensional QoL scale cancer version • Advanced care planning • Resource utilization • 6 clinic visits, hospital stay, ED visits	• Dyspnea improved OR 6.7 (1.04-35.6) • No change in pain • Primary care physicians did not follow recommendations often • Greater spiritual well-being • No difference in health care satisfaction, advanced directives • No difference in resource utilization • No difference in RN charges $47,211 (SD 73,009) *vs.* $43,858 (SD 69,647)	• Imbalances in groups • Attrition below power (50 per group) • Skewed economic outcomes • Multiple outcomes without correction • Dependence on primary care physicians to implement changes
Zimmermann *et al.* (21) [2014]	Advanced cancer prognosis 6-24 months	• Palliative care consultation and continuity • Palliative care specialist • Nurse specialist • Monthly follow up • 24-hour service	Usual care	• FACIT—spiritual well-being • QoL and end of life • ESAS • FAMCARE-P16 • Cancer Rehabilitation Evaluation System Medical Interaction Scale	• FACIT-SP—not different at 3 months (primary end point) • ESAS—not different at 3 months • FACIT-SP—improved at 4 months • All secondary outcomes improved at 3 and 4 months	• Underpowered • Primary outcome not met • Correction for multiple outcome • Sensitivity analysis done • Mixed effect done for clusters
Rummans *et al.* (22) [2006]	Advanced cancer patients undergoing radiation	• Multi-disciplinary intervention • Eight sessions, 90 minutes • Cognitive behavior therapy • Exercise • Discussion • Radiation	Usual radiation care	• Spritzer QoL Scale • Linear Analog Scale—QoL • Symptom Distress Scale • Profile of Mood State • FACIT—Spiritual Well-Being	• Improved QoL-responders analysis • NNT-5 • 9 point difference • Improved spiritual well-being • Differences at 4 weeks but not 8 to 27 weeks • Multiple secondary end points positive	• Responder's analysis for primary end point • Therapeutic benefit lost at 8 weeks

Table 2 *(continued)*

Table 2 *(continued)*

Reference	Patient	Intervention	Controls	Outcome measures	Results	Comments
Meyers *et al.* (23) [2011]	Advanced cancer patients and caregivers	• Cognitive-behavior • Problem solving education program • Three sessions within 30 days	Usual care	• City of hope—QoL instruments for patients and caregivers • Social problem-solving inventory revised	• No difference in QoL • Caregiver QoL decreased at less than half the rate with intervention • No difference in problem-solving • Caregiver QoL effect size—0.3 SD	• Attrition reduced power to 0.48-0.51
Toseland *et al.* (24) [1995]	Cancer patient caregivers Patients had to be >3 months from diagnosis	• Social worker • Lead spousal education on caregiving • Six sessions, each 1 hour	Usual care	• CES-D-depression • State-trail anxiety intervention • Dyadic adjustment scale marital relationship • Social Functioning Subscale of the Health and Daily Living Form • Medical Outcomes Study—SF20 • Zarit Burden Inventory • HELP seeking coping index • Index of Coping Responses • Pressing problems • Alcohol use • Patient assessment with FIIC and ECOG	• No significant difference • Some benefit in a subset of distressed caregivers	• Small number of dyads [80] for outcomes

FACT-L, functional assessment of cancer therapy-lung; QoL, quality of life; HADS, Hospital Anxiety and Depression Scale; PHQ, Patient Health Questionnaire; TOI, trial outcome index; COPD, chronic obstructive pulmonary disease; SF, short form; ESAS, edmonton symptom assessment scale; CES-D, center for epidemiologic studies depression scale; ED, emergency department; ICU, intensive care unit; ADL, activities of daily living; NRS, numerical rating scale; SE, side effects; RN, registered nurse; SD, standard deviation; FACIT, functional assessment of chronic illness therapy; FACIT-SP, functional assessment of chronic illness therapy-spiritual well-being scale; NNT, number needed to treat; FIIC, functional living index-cancer; ECOG, Eastern Cooperative Oncology Group.

Table 3 Randomized trials of home palliative care

Reference	Patient	Intervention	Controls	Outcomes measures	Results	Comments
Hughes *et al.* (25) [2000]	VA patients severely impaired or terminal illness	• Team managed • Systematic screening • Continuous patient care management by physician at home • Visits based on need	Continuity within VA outpatient	• Barthel Index Function • Medical Outcomes Study—SF-6 • Caregiver QoL Wave Satisfaction with Care Scale • Health Care Costs • Smith Comorbidity Index—re-hospitalization • Short Portable Mental Status Questionnaire	• No difference in function • Terminal patient had ↑ QoL • Individuals with impaired ADL had ↑ satisfaction • Caregivers of terminal patients has ↑ QoL • No difference in re-hospitalization • Cost of care for home care 12% higher at 12 months	• No intention to treat analysis • No definition of terminal illness • Cost *vs.* charges • Indirect cost for non-VA utilization o Estimated costs • Self-reported data—20% for costs • Benefits not sustained past 6 months • Costs did not include palliative care service
Grande *et al.* (26) [1999]	Hospital at home for terminal patients—prognosis ≤2 weeks	• Home nursing care up to 24 hours	Standard care	• Dying at home	• Dying at home not different • Those who made it home were more likely to die at home	• Underpowered imbalances between
Hughes *et al.* (27) [1992]	Terminally ill patients (<6 months survival) and caregivers	• Hospital-based Home care • Multidisciplinary • Inpatient and outpatient	Standard post hospital care	• Barthel Self-Care Index • Short Portable Mental Illness Questionnaire • OARS Multi-dimensional Functional Assessment Questionnaire • Philadelphia Geriatric Morale Scale • Satisfaction with Care Scale • Resource utilization	• More home visits 19.2 *vs.* 13.64 days • Longer length of stay with home care 67.9 *vs.* 46.1 days • No difference in survival (76 *vs.* 83 days) • No difference in ADL, morale cognition • Improved satisfaction, reduced caregiver morale	• Imbalances • Same hospital deaths • Home care costs greater with home care • Healthcare resource utilization did not take into account costs related to maintaining the intervention • Reduced cost—18%

Table 3 (*continued*)

Table 3 *(continued)*

Reference	Patient	Intervention	Controls	Outcomes measures	Results	Comments
McCorkle *et al.* (28) [1989]	Lung cancer home bound stage II, III, IV	• Nurse Specialist Home Care	Standard home care (non-specialist) and office outpatient care	• Symptom Distress Scale • McGill/Melzack Pain Questionnaire • Profile of Mood State • Enforced Social Dependence Scale—Functional Status • General Health Rating index • Health Care Resource Utilization	• No difference between specialist home care and standard home care • Fewer hospitalization with standard home care • Length of stay in hospital not different • Claim of reduced costs with specialist home care	• Study patients differed from general registry patients • Imbalanced groups • Not intention to treat analysis • No dollar amount given for resource utilization
Zimmer, Groth-Juncker and McCusker. (29) [1985]	2 groups—Terminally ill with ≤3 months life expectancy; Chronic home bound ill	• Home health team o Nurse o Physician o Social Worker o 24-hour call availability	Standard care	• Health care utilization-diary • Sickness impact profile • Philadelphia geriatric center morale scale • Patient and caregiver satisfaction • Death at home	• Fewer hospital days and nursing home stays • No difference in sickness impact or morale • Cost of care not different at 90 days • More deaths at home with homecare (71% *vs.* 47%) • Greater satisfaction	• Underpowered • Imbalance in groups
Kane *et al.* (30) [1984]	Advanced cancer patients with 2-6 weeks survival plus caregiver	• Home hospice	Standard care	• California pain assessment profile • CES-D • General well-being assessment—anxiety satisfaction • Costs	• 60% died in hospice *vs.* 80% died in hospital • No difference in inpatient days, ICU, cost improvement satisfaction	• Balanced groups
Cummings *et al.* (31) [1990]	VA patients either severely disabled or survival <6 months	• Hospital-based home care (see Hughes S) • Interdisciplinary team	Standard care	• Barthel self-care index • Short portable mental status questionnaire • Philadelphia geriatric center morale scale • Satisfaction with care scale • Cost and service utilization	• Survival the same • No difference in ADL, morale or satisfaction • Average cost of care reduced 13% but not significant • Total hospital days not different	• Imbalanced groups

Table 3 *(continued)*

Table 3 *(continued)*

Reference	Patient	Intervention	Controls	Outcomes measures	Results	Comments
Grande *et al.* (32) [2000]	Terminally ill patients <2 weeks survival: motor neuron disease; cancer; AIDS	• 24-hour practical nurse care at home	Standard care (care in hospital or hospice), MacMillan nurses, private care, flexible care, nursing service	• Need for more help • Symptom severity • Time spent at home • Place of death • Non-validated questionnaire • Completed by GP, district nurse, caregiver	• No difference in symptoms, except pain • No difference in visits in last week • No difference in input from other services • GP felt more anxiety occurred in control carers • District nurses—felt caregivers needed more help in controls • Carers felt that there was more nausea and pain in controls	• Referral dependent accrual • Controls had variable care • Not ITT-large attrition • Imbalances between groups • No real reduction in service utilization
Brumley *et al.* (33) [2007]	Advanced cancer COPD Heart failure PPS ≤70%	• In home palliative care • Continued disease modifying therapy • Palliative care physician coordinates care • Interdisciplinary team	Usual care	• Satisfaction Reid-Gundlach • Satisfaction with service instrument • PPS • Resource utilization • Hospice enrollment	• Improved satisfaction • Reduced ED and hospitalization • In home palliative care accounted for 14% of variance in hospital days • Mean cost reduction $7,552 (SD 2,374-12,730) • 71% in in-home palliative care died at home *vs.* 51% of usual care • 2.2 times more likely to die at home with adjustments • Overall costs decreased 35% • 25% of in-home palliative care entered hospice *vs.* 33% usual care	• Survival reduced in home palliative care 196±164 days *vs.* 242±200 days (P=0.03) • Cost not charges • Cost of service not included
Jordhøy *et al.* (34) [2000]	Advanced cancer	• Palliative care consultations and coordination of home care with local physician and district nurse • Education of community staff	Conventional care	• Place of death • Days spent as inpatient the last month of life • Health related QoL	• Survival 99 days in interventional and 127 days control (P=0.1) • More deaths at home 25% *vs.* 15% (P=0.02) • Fewer nursing home deaths 9% *vs.* 21% (<0.01) • Hospital deaths not different • Admission in the last month was less 13% *vs.* 24% (P<0.01)	• Imbalances in groups

Table 3 *(continued)*

Table 3 *(continued)*

Reference	Patient	Intervention	Controls	Outcomes measures	Results	Comments
Uitdehaag *et al.* (35) [2014]	Un-resectable or recurrent upper GI cancer	• Home visits by nurse specialists	Conventional outpatient follow up	• Euro QoL-5D-QoL • EORTC-QLQ-C30-QoL • Satisfaction resource utilization	• No statistical difference in QoL • Patient and relative satisfaction better • Higher cost with intervention • No difference in hospitalization	• Powered • Subgroup with 4-6 months follow up
Molassiotis *et al.* (36) [2009]	Colorectal and breast cancer patients receiving capcitabine	• Specialist nurse	Standard care	• Self-assessment • Chemotherapy • Toxicity • Inpatient days	• Reduced mucositis, constipation, nausea, pain, fatigue • Reduced in-patient days 57 *vs.* 167 days	• Supportive care at home during chemotherapy
Hudson *et al.* (37) [2013]	Caregivers of advanced cancer patients receiving home palliative care	• Family caregiver support nurse • Psycho-education resource • Home-visits • Assess unmet needs • Plan of care with home palliative care team	Usual home care	• General health questionnaire-psychological distress • Caregiver competency • Family inventory of need	• Not statistically different in psychological distress • Improved preparedness and competence with more extensive intervention (2) small effect size (0.29-0.144) • No improvement in unmet needs or caregivers positive conception of role	Powered accrual met

VA, veterans administration; QoL, quality of life; OARS, older Americans' resources and services; ADL, activities of daily living; CES-D, center for epidemiologic studies depression scale; ICU, intensive care unit; GP, general practitioner; ITT, intention to treat; COPD, chronic obstructive pulmonary disease; PPS, palliative prognostic score; ED, emergency department; GI, gastrointestinal; EORTC-QLQ, European Organization for Research and Treatment of Cancer Study Group-QLQ-C30.

from the same study but involved different outcomes and so reported separately on *Table 2*. In addition seven systematic reviews obtained and outcomes summarized (*Table 4*).

Results

The results of this systematic review are summarized on *Tables 2-4*. In this review of randomized controlled trials testing the intervention of early palliative care in various settings and populations, a multitude of advantages have been demonstrated. These advantages include improvement in certain symptoms such as depression, improved patient quality of life, reduced aggressive care at the end of life, increased advanced directives, reduced hospital length of stay and hospitalizations, improved caregiver burden and better maintenance of caregiver quality of life and reduction in the medical cost of care as well as patient and family satisfaction (*Tables 2-4*) (8-10,14,17,19,21,22,45,46). Yet there were randomized trials which demonstrate that symptoms are not improved, quality of life is not improved, and resource utilization and costs are not different from "usual" care (11-13,15,16,18,20,23,24). The same mixed findings are observed in randomized trials of palliative homecare services (*Table 3*) (25-37,41). Seven systematic reviews of randomized trials came to similar conclusions, with mixed findings in terms of palliative care benefits (*Table 4*) (38-44).

Why are there differences in the benefits to palliative care in randomized control trials?

There are notable methodological issues that may account for differences in findings among the randomized control trials of early palliative care. First, the structure of the interventions often consisted of a single professional and/or variably other professionals who were directly involved in patient care or in providing care continuity but not a full multidisciplinary palliative care team (11-13,16). Even if a multidisciplinary team regularly saw patients as an outpatient, recommendations were not be followed by those responsible for the direct care of patients diminishing the impact of the intervention (20). The palliative care consultative team was dependent on the primary physician to implement recommendations. Compliance to such recommendations were in fact be variable and influence outcomes. This may explain differences between two studies with the same intervention by design but with different outcomes (8,20).

Another methodological issue which occurred across all studies was the definition of "usual" or "standard" or "conventional" care. There were no descriptions of what was meant by "usual" care. Usual or conventional care is regionally-dependent and is provider-dependent. There was no mention of guidelines on "standard" practice. Negative findings may have been that usual care was not much different from the palliative intervention or in the opposite manner, suboptimal which would have diminished or magnified the interventions benefits respectively. In at least one study the "standard" of care changed in the middle of the study (12).

Furthermore, study designs and procedures were frequently flawed. Participants were referred or recruited rather than consecutively screened for eligibility. Referral based studies would potentially recruit a biased population, providing a convenient sample population which passed physician gatekeeping, but would not likely represent the population and thus limit generalizability (47). Imbalances between randomly-allocated groups were not infrequent (12,16,20,38). Blinding of the investigators assessing outcomes is reported in only a minority of studies (21). Power calculations for accrual based upon the primary outcome was performed in a minority of studies. Additionally, many studies were underpowered due to attrition and because outcomes were frequently multiple (11,13,19,21,23). This would increase the risk of a type II error. The median attrition rate reported in one systematic review was 40% (42). Other methodological concerns include issues related to the timing of assessment of outcomes. For example, improvements in the primary outcome in one trial were detected later than anticipated in the original design (21). In another trial the benefit to the primary outcome was transient (22). Other methodological issues include the fact that analyses frequently did not include all randomized participants, with most trials employing per protocol analyses (12-14). Only one study reported outcomes with a responder's analyses with a significant improvement in the primary outcome measure in terms of numbers needed to treat (22,48). Sensitivity analyses was done in only a few studies. Few mentioned how missing data was handled. Some of the studies used words like "trends" for a non-significant outcomes or "near significant" findings which may have been a "spin" on the outcomes to place the study in a favorable light (49).

Definitions of "early" palliative care

Other issues likely influencing the variable findings of

Table 4 Systematic reviews of palliative care service trials

Reference	Search	Trials	Outcomes	Comments
El-Jawahri *et al.* (38) [2011]	• 1 from 1984 up to 2011 • Terminally ill patients • Palliative care	• 17/18—QoL primary outcomes • 18—QoL secondary outcomes • 15—symptoms • 12—psychosocial symptoms • 6—family caregiver • 10—satisfaction	• QoL o 3/7 adequately powered with primary outcomes o 5/7 statistically significant improved • None looked at clinically meaningful change o 7/8 with QoL as secondary outcome failed to show difference • Physical symptoms o Little evidence of reduction in physical symptoms o 9 trials involved interventions without direct patient care • Psychological symptoms o 6 trials demonstrated statistically important improvement • Family caregiver o 5 trials demonstrated improved caregiver QoL, depression, anger after death bereavement, burden • Patient/caregiver satisfaction o 7 demonstrated improved satisfaction	• Failure to improve QoL as secondary outcome may be related to power • Challenges o Recruitment versus screening o Economic outcomes o Imbalances in some studies o Little evidence for improvement in physical symptoms
Shepperd *et al.* (39) [2011]	• Hospital at home care 1950-2011 Cochrane Review Terminally Ill	• 4 trials	• Home care based services are associated with more deaths o RR1.33 (95% CI: 1.14-1.55) • No improvement in function psychological well-being, cognition • Little impact on caregivers • Some improvement in satisfaction	• Wide variability in service structure o Heterogeneity prevents conclusions
Fergenbaum *et al.* (40) [2015]	• Heart failure • Home care	• 6 trials o Care at home by single health care professional o Nurse led care education o Pharmacist led care at home	• Meta-analysis o Decreased risk of mortality OR 0.88 o Reduced hospitalization OR 0.92 (95% CI: 0.80-0.97) o No reduction in overall mortality o Fewer ED visits (–1.32/95% CI: –1.87-–0.77) o Care at home savings $10,655 and 0.11 gain in QALY	

Table 4 (*continued*)

Table 4 (*continued*)

Reference	Search	Trials	Outcomes	Comments
Gomes *et al.* (41) [2013]	• Home palliative care Cochrane database review	• 16 RCT • 7 controlled trials o 37,561 participants o 4,042 families • Caregivers • Patients with cancer, HIV, COPD, heart failure, multiple sclerosis	• Meta-analysis o Odds of dying at home 2.21 (95% CI: 1.31-3.71) o NNTB-5 o NNTR—including only high quality RCT 1.28 • Symptom burden o Reduced o Small effect (0.08 for scale 0-7), 2.1 for scale 0.20 o No improved pain overall • Physical function o 3 RCT negative o 2 RCT positive • QoL o 2/7 statistically unknown o 3/7 negative o 2/7 certain dimensions improved • Caregiver burden o 2 RCT conflicting results o 1 negative study o 2 positive studies • Caregivers grief o Strong evidence for no benefit • Satisfaction o 3 RCT positive o 2 RCT negative • Deaths in Institution o Marginal benefits o Hospital variable or between 0.02-0.99 o NH deaths OR 0.64 (0.4-1.03) No difference in advanced care planning resource utilization, hospice referral, family absenteeism from work	• Cost and cost effectiveness was evaluated in 7 RCT and one controlled study. All six studies demonstrated some reduced costs (18-36%) statistical significance was seen in only one o Some reported skewed data using the mean o Few transformed data

Table 4 (*continued*)

Table 4 *(continued)*

Reference	Search	Trials	Outcomes	Comments
Zimmermann *et al.* (42) [2008]	• 1984-2007 palliative/ terminal patients	• 22 RCT median sample size 2007 [69-4,804] o 4 cluster RCT o 11 exclusively cancer o 2 geriatric o 12 multi-disciplinary intervention o 3 care coordination by nurse or social worker	• QoL o 9/13 trials were negative • Symptoms o 13/14 studies were negative o 3 studies savored intervention for symptom distress but not severity • Satisfaction o 6/10 trials were negative • Caregiver satisfaction o 7/10 trials positive • Resource utilization o 7/22 economic outcomes o 16/22 resource utilization without cost analysis o Only 1 US study was positive but suffered from imbalance o 1 VA study demonstrated increased costs • Hospitalization o 1/9 studies had demonstrated reduced hospitalization	• Lack of power for many studies • Lack of adjustment for attrition • Imbalances between groups • Failure to define primary measure • Cluster randomization with only 2 clusters • Failure to correct for multiple outcomes • Economic outcomes often did not include cost of intervention, indirect costs, family costs (lost wages, lost savings) • Blinding as to allocation for assessors—9/22 studies • 3/11 meet accrual based on power calculations • Median attrition 40% (9-92%) • Contamination of controls with intervention due to same location of care • Definition of usual care not provided in any study
Higginson and Evans. (43) [2010]	• 2000-2009 specialist palliative care and cancer	• 40 trials o 8 RCT o Multiple areas (home, hospital, inpatient units)	• Mixed benefits for pain, symptoms, satisfaction, reduced hospitalization • No adverse effect of palliative care compared to usual care • Some suggestion of lower costs • QoL less often different between intervention and usual care and diminished over time	• Imbalances • Biases in all studies • More work needed to detect which components of palliative care have an impact • Studies were largely in urban centers and few were multicenter • Need to investigate what skill sets and team mix works for best effect o Single professional o Team of nurse and physician o Multidisciplinary team

Table 4 *(continued)*

Table 4 *(continued)*

Reference	Search	Trials	Outcomes	Comments
Luckett *et al.* (44) [2014]	• Palliative care models 2001-2014	• 9 RCT • 34 controlled trials • Systematic reviews averaged 18 studies	• Home based care models o Stated effectiveness in communication enhanced skills of GPs, caregivers o Clarity goals of care o Outcomes—avoid aggressive care at EOL • Acute care models o Consultation or inpatient care o Outcomes were prognosis, goals of care, forgoing aggressive care, family/patient support, discharge planning, symptoms, economic savings • Emergency room (ED) o Symptoms, length of stay, economics, admissions • Residential elder care o Outcomes were communication symptoms, advanced directives, inappropriate hospitalization, identifying residents appropriate for palliative care • Transitions of care o Outcomes were community hospital, elder care continuity, communication of goals, management plans	• Heterogeneous population • Different focus/model based on care setting • Lumped all diagnosis together when measuring effectiveness • Poorly defined palliative phase of care • Variations in content of models per setting • Lack of detailed reporting • Description of models and intervention heterogeneous • Few studies across settings • Cost effectiveness is greatly influenced by survival, controversy about the method of cost accounting often not patient centered or family centered • Cost accounting if more often centered on cost and not efficacy/efficiency reduced cost alone may be inadequate • There is not data on cost-effectiveness on different models of care

Table 4 *(continued)*

Table 4 *(continued)*

Reference	Search	Trials	Outcomes	Comments
Luckett *et al.* (44) [2014]			Types of models • Case management o Patient centered o Family/patient plays a large role in service structure o Difficult to do controlled studies • Shared care o Identify lead clinician working with other clinicians o Focus on communication o Rapid needs based response o In rural areas—"trigger" for shared care • Specialist outreach o Clinics within primary care, cancer centers, rural areas o Multifaceted care o Overlap with shared care • Managed clinical networks o Underserved population o Clinical networks o Access links primary, secondary, tertiary care o Overlaid in pre-existing system o Funding is geographically confined, system confined • Integrated care o Conjoining different services for collaboration o Continuity, synergy o Needs based	

QoL, quality of life; ED, emergency department; QALY, quality of life years; RCT, randomized controlled trial; HIV, human immunodeficiency virus; COPD, chronic obstructive pulmonary disease; NNTB, number needed to treat to benefit; NH, nursing home; VA, veterans administration; EOL, end of life.

studies in early palliative care include the definition of "early" palliative care which has been variously constructed. In the study by Dr. Temel and colleagues, the definition of "early" palliative care for lung cancer was at the time of diagnosis of advanced cancer and nearly simultaneously with the initial oncologic consult; the initial location of consultation and continuity was provided in the outpatient setting (8). Others have defined "early" palliative care as being seen less than 3 months after diagnosis of advanced cancer (50) or as being seen by a palliative care specialist greater than 3 months before death (51). Another timeframe for "early" palliative care in the setting of advanced ovarian cancer was at the time of cis-platinum resistance (52). Additionally, the definition of "early" palliative care has been tied to the presence of certain prognostic signs and symptoms (53). "Early" palliative care has also been defined by where the palliative consultation takes place; outpatient versus inpatient (54). Another definition was based on the duration of continuity (greater than 90 days, 31-90 days, 11-30 days and 1-10 days) before death (55). Hence, there is no universally accepted definition of "early" palliative care which complicates assessment of early palliative care benefits. Based upon randomized trials, it does appear that for full benefits of palliative care to be realized, continuity by a multidisciplinary team is needed for at least 3-4 months (8,21,45).

Definitions of patients eligible for palliative care

There is also variation in the definition of palliative care when reviewing home palliative care services. Patients with heart failure or chronic obstructive lung disease were considered for homecare if admitted to the hospital twice or intensive care stay once (56,57). Admission to palliative homecare was based on various periods of time; survival expectation of less than 24 months, expected survival of 12 months, expected survival of less than 6 months or less or even imminently close to death (2 weeks) (12,31-33,58,59). Alternatively, impairment of activities of daily living or been homebound status with heart failure, chronic obstructive lung disease or a terminal illness were criteria for initiation of palliative homecare (25). As a result, optimal timing for initiating palliative homecare cannot be determined on the bas based on randomized control trials.

Another likely contributor to the heterogeneity of findings across studies of early palliative care is the heterogeneity of palliative care models that have been used in the randomized control trials. Each location of care may have a different important outcome (inpatient care, inpatient consultative services, outpatient integrated care and home care) (44). There is little evidence to guide interventionists in their choice of the most effective model of care.

Models of palliative care

Population heterogeneity in many the trials may have confounded outcomes. The assumption that the same model of care was equally effective across different diseases is unsubstantiated. In addition there is a poor definition of the "palliative" phase of illness. Certain models of care may work better at different phases of illness, early versus late cancer for instance or in different diseases or disease trajectories. The hospice case management model is used at the end of life and shared care or integrated care or consultative models are frequently adopted in palliative care. Models of care may also depend on cultural and ethnic background, family dynamics and patient location. Referring specialists may have a preference for engagement and timing of referral which will influence care models. There are few comparative trials of palliative care models with reasonable quality. There is some evidence that in-patient palliative care provided better pain control than home care of conventional hospital care, but this research is limited and open to criticism (60). Research on palliative home care teams and coordinating nurses has demonstrated limited impact on quality of life over conventional care for patients dying at home. These negative findings are due in part to the limitations in the assessment tools (60). There is a need for other larger studies to provide clear evidence as to whether specialist palliative care services provide improvements in patients' quality of life. Few studies cross service lines (inpatient to outpatient to home care) which patients frequently do with life limiting illnesses. Models of care within randomized studies frequently were described vaguely and in less than optimal detail (44). And at the present time there is no data on the cost-effectiveness of different models of palliative care (44).

The price of palliative care: is there a benefit?

The gold standard for cost-benefit research involves changes in healthcare resources (personnel, materials, equipment and facilities) where expenditures are offset by reductions in spending for other medical services (61). The published data of cost benefit analysis in randomized trials of palliative care have focused exclusively on patient medical costs with mixed results. The variability within groups is wide; the standard deviation is larger than the mean (wide coefficient of variation) indicating lack of precision and skewed economic data; it is likely that outliers played a role in determining economic outcomes since all studies used the mean as a comparison (14,17,20). Cost-of-illness estimations were used in a heterogeneous population of terminally ill patients which included cancer, heart failure and chronic obstructive lung disease (17). However, the cost-of-illness studies should use event-costs from populations with similar diseases (62). Many studies have suggested that palliative care reduces hospitalizations and aggressive interventions at the end of life. However, these studies did not directly measure cost and rather assumed an economic benefit associated with reduced aggressive care at the end of life (8). Some have demonstrated that palliative interventions and advanced directives do not reduce medical costs (16,20,30). Many of the studies did not include the cost of the intervention in their analyses of benefit or it is not mentioned in the manuscript (17,20). One study demonstrated higher costs with the intervention (35). Current studies fall short of the goal of measuring all relevant factors to assessing costs-benefits and instead have focused narrowly on patient medical costs. A classification of palliative care costs-benefits involves four categories: (I) patient medical factors which involve improved quality and quantity of life cost of medical care services; (II) patient nonmedical factors include changes in workplace productivity and accommodation by employers; (III) family medical factors which include changes in quality of life of family members and changes in healthcare use by family members; (IV) family nonmedical factors which include changes in workplace productivity and school performance of family members (61).

Typical methods for estimating costs involve examination of gross charges and applying a "cost to charge" ratio to estimate costs. However, in health care reimbursement charges often bear little relationship to costs. Hospital charges may exceed costs by a factor of two or more. In the same manner, actual reimbursements are at best a good approximation of costs (61). Several studies have shown that palliative care improves the quality of life of patients. This has not been integrated into cost benefit studies as a quality adjusted life year analysis. The commonly used instruments in palliative care which measure quality of life have their roots in psychometrics; they are not designed for health care utility but rather as a measure of human characteristics. There is a need to construct new quality of life scales in palliative care to be consistent with economic theory if it is to be used in a cost-effective analysis. Providing end of life care is unique enough in achieving "a good death" that a condition specific measure for cost-effectiveness in needed. Providing a good death, for example, may reduce health problems of the surviving spouse and hence have an economic benefits which is indirect (61).

The National Institute of Health has reported that costs associated with workplace productivity loss can exceed the direct costs of medical care for many chronic illnesses (61). In the study reported by Dr. Addington-Hall and colleagues, 38% of family spent their life savings on end of life care for their loved ones in part related to loss of income and increased medical expenditures needed at the end of life for their loved one (16). A recent study found that the cost of caregiving was significant leading in some instances to family debt or bankruptcy. Direct costs to families include transportation, food and medication; indirect costs were loss of employment or absenteeism (family medical leave), cultural and caregiver stress, burden and impaired health. The palliative care context in this study increased costs, as the goals of meeting patient needs were prioritized over the cost of care. In a similar manner reducing the length of stay in the hospital may in fact increase family and caregiver costs (63). Research is desperately needed to quantify the financial contribution of families to palliative care and the effect of palliative care on the financial health of the family. It is important as palliative care becomes integrated early into the care of serious illnesses that a uniform model of care be developed for each stage of disease and that the model be adapted to the trajectory of disease.

Future direction in research

Complex interventions are intrinsic to multidisciplinary palliative care services and palliative care as integral with other services to the care advanced illnesses. Complex interventions involved multiple interacting components each of which contribute to the outcome. Careful modeling of complex interventions is essential in healthcare services research. Such research requires formal feasibility studies of each component and a mixed method design which includes qualitative research techniques (64-66). Qualitative outcomes are used to confirm quantitative findings and to place quantitative findings in context within a study. Qualitative techniques can be used to determine why one component of an intervention works and another does not work. Unfortunately qualitative research methods are rarely incorporated into randomized trials. It would be important in future palliative care service research trials to incorporate qualitative methods to fully assess quantitative outcomes.

Most randomized trials of palliative care services have been parallel in design. However, other methods of testing palliative care services could involve stepped wedge designed trials where the intervention is rolled out over time to a larger number of individuals. Comparisons are made between those receiving the intervention and those who are still receiving standard care (67). The other alternative is fast-track randomization where a group of individuals are randomized to receive the intervention and a group who well in the future cross over to the intervention. The benefits of the intervention are measured at the time of crossover. The crossover has to be delayed long enough to allow the intervention benefits to be fully realized but short enough to minimize attrition (68-70). Both methods allow all participants to receive the benefits of palliative care but would also adequately test the benefits of early palliative care.

Conclusions

Recent randomized trials of palliative care as an integrated intervention early in that trajectory of a life limiting illness has variably demonstrated benefits to patient and caregiver wellbeing and to health care utilization. These findings point to the benefits of involving multidisciplinary palliative care teams early in the course of serious illness. However, notable limitations to these studies highlight the need for further evidence. We need an evidence-based definition of “early” palliative care to determine the optimal timing to intervene. Furthermore, studies are needed to determine what models of care are effective and to define the best models of care for variable populations (e.g., inpatient *vs.* home care) and disease types. Finally, the economic impact of palliative care should be assessed in a manner that includes all medical (including the cost of the palliative care intervention) and non-medical factors contributing to costs. With a rigorous evidence-base guiding its development and implementation, effective models of palliative care can be delivered at appropriate time points in the course of illness, to the betterment of patients, families, and health care systems.

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Footnote

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