QUERI

Integrated Outpatient Palliative Care in Oncology

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PREFACE

The VA Evidence-based Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of particular importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. QUERI provides funding for 4 ESP Centers, and each Center has an active University affiliation. Center Directors are recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Centers. The ESP is governed by a Steering Committee comprised of participants from Veterans Health Administration (VHA) Policy, Program, and Operations Offices, VISN leadership, field-based investigators, and others as designated appropriate by QUERI/HSR&D.

The ESP Centers generate evidence syntheses on important clinical practice topics. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The ESP disseminates these reports throughout VA and in the published literature; some evidence syntheses have informed the clinical guidelines of large professional organizations.

The ESP Coordinating Center (ESP CC), located in Portland, Oregon, was created in 2009 to expand the capacity of QUERI/HSR&D and is charged with oversight of national ESP program operations, program development and evaluation, and dissemination efforts. The ESP CC establishes standard operating procedures for the production of evidence synthesis reports; facilitates a national topic nomination, prioritization, and selection process; manages the research portfolio of each Center; facilitates editorial review processes; ensures methodological consistency and quality of products; produces “rapid response evidence briefs” at the request of VHA senior leadership; collaborates with HSR&D Center for Information Dissemination and Education Resources (CIDER) to develop a national dissemination strategy for all ESP products; and interfaces with stakeholders to effectively engage the program.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP CC Program Manager, at Nicole.Floyd@va.gov.

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This report is based on research conducted by the Evidence-based Synthesis Program (ESP) Center located at the **Durham VA Medical Center, Durham, NC**, funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Quality Enhancement Research Initiative. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (*eg*, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

STAKEHOLDER AND TECHNICAL EXPERT PANEL

In designing the study questions and methodology at the outset of this report, the ESP consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

The list of stakeholders and members of the Technical Expert Panel (TEP) who provided input to this report follows.

Stakeholders

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INTRODUCTION

Each year in the United States, more than 500,000 Americans, including 40,000 Veterans, are diagnosed with advanced cancer.[1] Cancer is associated with various physical symptoms including pain and may affect quality of life (QOL), functionality, psychological health, and family systems.[2] Palliative care services assist with managing physical symptoms and emotional, psychosocial, and spiritual distress of patients with serious illnesses such as cancer. Palliative care ideally begins at the time of diagnosis of a serious illness and continues until the end of life; it is appropriate at any stage of illness and can be provided along with curative treatment.[3] Although primary care practitioners and oncologists have always incorporated palliative care into their treatment of patients, palliative care has become a specialty recognized by the Accreditation Council for Graduate Medical Education with board certification through the American Board of Internal Medicine.[4]

Many Veterans receive their treatment and supportive care services through the VHA, where palliative care services are often integrated with oncology care services during an inpatient hospital stay. All enrolled Veterans in the United States have access to palliative care during an acute VA hospital admission, which frequently addresses issues related to uncontrolled symptoms and goal-setting. Such integration of palliative care services with disease-directed care is now considered standard of care for patients with advanced cancer, guided by the recommendations of many influential cancer advocacy and membership organizations. Both the National Academy of Medicine and the American Board of Internal Medicine identify palliative care as integral to improving the quality of cancer care.[5,6] Further, the American Society of Clinical Oncology has released both a provisional clinical opinion[7] and a recent guideline[8] calling for the regular integration of palliative care into standard oncology care. The Oncology Nursing Society has a similar position, recommending early integration of palliative care for patients with cancer.[9] In addition, the American College of Surgeons' Commission on Cancer requires that cancer centers have access to palliative care services to be accredited by American College of Surgeons.[10] Furthermore, the National Comprehensive Cancer Network[11] has incorporated early palliative care integration into their evidence-based pathways for the routine care of patients with advanced cancers or high distress. To date, several clinical trials have demonstrated the value of this integrated approach to improve several cancer-related outcomes, including patient and caregiver satisfaction with care,[12] health-related QOL,[13] and potentially overall survival.[14] Both a recent meta-analysis/systematic review[15] and a Cochrane Collaboration review[16] report consistent and significant improvements in patient QOL, symptoms, and caregiver mood across disease types and settings, demonstrating the applicability of these findings across multiple venues in which cancer patients receive care.

Increasing recognition of the value of specialty palliative care services has led to dramatic growth in the field as well as improvement in access to services. The clinical field of specialty palliative care has expanded by almost 150% across the United States in the last decade.[17] Consultation services are available at 66% of all US hospitals, including 98% of National Cancer Institute (NCI)–designated cancer centers.[18] This is a significant increase from an earlier report that demonstrated only 33% of NCI institutions having access. While palliative care has undergone increased acceptance and expansion, the nature of its integration with oncology

services remains understudied and unclear. Palliative care can be delivered in inpatient as well as outpatient settings. Most palliative care services can be delivered by primary physicians or oncologists; however, specialty palliative care consultation teams that demonstrate significant variability in team composition, penetration of services among hospitalized patients, and outcomes related to financial savings to health systems are common.

Although integration of services is recommended for all patients with advanced cancers or high medical needs, uncertainties remain. For example, the majority of patients included in palliative care clinical trials have non–small cell lung cancer and, to a lesser extent, non-colorectal gastrointestinal cancers. Thus, the applicability of these trials' findings to other common cancer populations within VA, such as prostate and head and neck cancers, is not clear. Also, the most effective route to deliver palliative care interventions remains an open question. Some trials use a telephone-based approach, recognizing the need for distance-based education and follow-up for patients who live in rural communities and/or travel long distances for face-to-face care. Other trials use a more intensive, face-to-face approach, requiring a minimum number of visits within the trial. Further, the majority of participants in the palliative care intervention trials are white, raising questions about generalizability to nonwhite populations. Last, the ideal degree of integration has not been well described—particularly in complex health systems or among patients with multiple health care providers addressing serious illnesses in addition to cancer.

With the increase in availability of clinical palliative care services, organizations have tested and implemented varying degrees and types of integration with oncology care. These can be evaluated using common instruments, like the Integrated Practice Assessment Tool[19] based on the health care integration framework by Heath et al.[20] Adapted from this framework, levels of integration across palliative care and oncology have recently been proposed in the Collaborative Care Continuum framework by Kaufmann et al.[21] In addition to levels of integration, leaders have described various methods of integration of services, including co-rounding models for hospitalized patients, embedded or colocated outpatient clinical services, and standalone clinics or services.[22,23] Further, organizations have had positive experiences with integrated services limited to particular disease or conditions, types of therapy (*eg*, investigational agents or novel immunotherapy drugs), or by embedding palliative care experts into non-patient-facing case discussions such as multidisciplinary oncology team meetings ("tumor boards").

In addition to other types of integration, much focus has been on the outpatient setting, which is where the majority of cancer care is delivered. For palliative care, the outpatient realm has been considered the "next frontier" of community-based palliative care services,[24,25] and although growth is robust, many communities do not have access to non-hospital services.

Currently, all VA hospitals have inpatient access to palliative care programs for hospitalized Veterans, yet significant gaps in services remain in the outpatient setting. Though evidence supports some type of integration, which types and which populations to target have not yet been clearly elucidated to the degree that policymakers in VA have actionable information on which to move forward. Palliative care integration may present opportunity costs that when weighed against expansion of other types of supportive care services (*eg*, behavioral health, navigation, genetic counseling) may not take priority.

We aimed to perform a thoughtful and careful systematic review to provide actionable information to VA physicians, leaders, and policymakers regarding the potential benefits of types of palliative care integration among the diverse population of Veterans with cancer.

METHODS

TOPIC DEVELOPMENT

This evidence report was commissioned to (1) evaluate the effects of palliative care, initiated "upstream," and integrated with oncology care for patients with cancer, (2) describe intervention characteristics associated with greater benefit, and (3) describe common barriers to implementing integrated palliative care into Veterans Affairs (VA) settings.

The key questions (KQs) for this systematic review were developed after a topic refinement process that included a preliminary review of published peer-reviewed literature, consultation with internal partners and investigators, and consultation with content experts and key stakeholders at the Association of VA Hematology/Oncology, Palliative Care Research Committee, the Office of Patient Care Services' Geriatrics and Extended Care Program, and the Hospice and Palliative Care Program.

The final KQs were:

KQ 1: In patients with symptomatic or advanced cancer, what are the benefits and harms of integrated outpatient palliative and oncology care compared with usual oncology care?

KQ 2: Which features of integrated palliative and oncology care are associated with greater benefit to patients with symptomatic or advanced cancer?

KQ 3: What are the most common and important barriers to implementing integrated palliative and oncology care in VA settings?

We followed a standard protocol for this review, and each step was pilot-tested to train and calibrate study investigators. The PROSPERO registration number is CRD42017057541.

SEARCH STRATEGY

In consultation with an expert librarian, we conducted searches of MEDLINE (via PubMed), the Cochrane Central Register of Controlled Trials, and CINAHL through November 21, 2016, for KQ 1 and KQ 2; through January 19, 2017, for KQ 3. We evaluated the bibliographies of systematic or nonsystematic reviews for relevant studies. We used a combination of MeSH keywords and selected free-text terms to search titles and abstracts. In addition, we reviewed the bibliographies of recent applicable reviews and contacted subject matter experts to identify additional studies.[15,16,26-28] All citations were imported into 2 electronic databases (for referencing, EndNote® Version X7, Thomson Reuters, Philadelphia, PA; for data abstraction, DistillerSR; Evidence Partners Inc., Manotick, ON, Canada). The exact search strategies used are in Appendix A.

STUDY SELECTION

Using prespecified eligibility criteria (Appendix B), 2 reviewers independently evaluated titles and abstracts to identify potentially eligible studies. Key eligibility criteria were randomized controlled trials (RCTs) or quasi-experimental studies evaluating integrated palliative and oncology care in adults with symptomatic advanced cancer; interventions delivered in outpatient

settings that addressed at least the physical symptom and psychosocial components of care; integration as evidenced by some degree of real-time communication between oncologist and palliative care team; and patient-reported QOL, survival, or health care utilization outcomes reported ≥28 days after enrollment. Because details of integrated care were routinely absent from the published literature, we provisionally included all studies meeting other eligibility criteria and attempted to contact all authors for missing information to inform final eligibility decisions. Four of 7 authors responded to these requests. When the information from the author differed from what could be ascertained from the article alone, this information was added. Studies addressing KQ 3, barriers to implementation, had to be conducted in the VHA or be related to a study included for KQ 1 and both quantitative and qualitative study designs were included. Articles included by either reviewer underwent full-text screening by 2 independent reviewers; disagreements were resolved by discussion or by a third investigator. Articles meeting eligibility criteria were included for data abstraction. Appendix C contains a list of excluded studies and the reason for exclusion.

DATA ABSTRACTION

Study characteristics including patient characteristics, intervention/comparator details, quality elements, and outcomes were abstracted into a customized DistillerSR database. To capture shorter- and longer-term effects, we abstracted outcomes at 2 timepoints: postintervention (±1 month) and at least 6 months' postintervention. For studies with multiple assessments at greater than 6 months postintervention, we abstracted the last available assessment. Because of diverse study designs, we abstracted data on barriers/facilitators to implementation of integrated palliative care into a structured report form that captured study design, population characteristics, key findings. All abstractions were overread by a second reviewer. Disagreements were resolved by discussion or by a third reviewer.

CATEGORIZATION OF THE INTERVENTIONS

We categorized the interventions along 2 dimensions: (1) 8 clinical elements of palliative care (*eg*, addressing physical and psychological symptoms) based on the Clinical Practice Guidelines for Quality Palliative Care as described by the National Consensus Project[29] (Appendix D) and (2) 7 elements of integrated care (*eg*, colocation, communication[19,20]) as measured by the Integrated Practice Assessment Tool (IPAT),[19] which is based on the Substance Abuse and Mental Health Services Administration's standard framework for levels of integrated health care.[20] The IPAT classifies practices into 6 levels, ranging from minimal collaboration to full collaboration in an integrated, colocated practice. The 6 levels are grouped as coordinated care (Levels 1 and 2), colocated care (Levels 3 and 4), and integrated care (Levels 5 and 6). In addition, we described the clinical disciplines delivering care and the mode of intervention delivery. Because information about integration was missing or unclear, we contacted the primary author for clarification; authors responded to our survey for 6 of the 9 studies (Appendix E). We used data from the authors and manuscripts to classify integration along a 6-level spectrum from "minimal collaboration" to "full collaboration in an integrated practice."

QUALITY ASSESSMENT

Quality assessment was completed independently by 2 investigators; disagreements were resolved by consensus or by arbitration from a third reviewer. We used the Cochrane risk of bias (ROB) tool for RCTs.[30] These criteria are adequacy of randomization and allocation concealment; comparability of groups at baseline; blinding; completeness of follow-up and differential loss to follow-up; whether incomplete data were addressed appropriately; and validity of outcome measures. For studies addressing implementation barriers, we used the revised Newcastle Ottawa Scale for cohort studies[31] and adapted the Critical Appraisal Checklist for qualitative studies.[32] We assigned a summary ROB score (low, moderate, or high) to individual studies.

DATA SYNTHESIS

We described the included studies using summary tables and graphical displays. We computed summary effects (*ie*, meta-analysis) when studies were conceptually homogeneous and there were at least 3 studies with the same outcome. We grouped outcomes into similar measurement windows (*eg*, 1-3 months after enrollment, 4-6 months after enrollment).

Some studies reported dichotomous outcomes (*eg*, survival) and some studies reported continuous outcomes (*eg*, QOL) or both. When quantitative synthesis was possible, we combined dichotomous outcomes using random-effects models and hazard ratio, risk ratio, or odds ratio as appropriate. Continuous outcomes were summarized using the standardized mean difference because outcomes were assessed with different measures for the same construct (*eg*, QOL). For analyses with few (n <20) studies, we used the Knapp-Hartung approach to adjust the standard errors of the estimated coefficients.[33,34] Sensitivity analyses included analyses that omitted studies judged to be at high ROB or that included only studies with relatively robust measures of the outcome. We evaluated for statistical heterogeneity using visual inspection and Cochran's Q and I^2 statistics. Publication bias was could not be assessed statistically because there were fewer than 10 studies in all analyses.[35]

We used a force-rank methodology that included presentation of initial rankings to stakeholders and study coinvestigators, followed by discussion, to identify the intervention and integration elements hypothesized to be associated with greater intervention effects. We used 2 rounds of iterative prioritization to select 5 intervention and 2 integration components for moderator analyses. Two of the intervention components (physical and psychosocial) were eligibility criteria and thus present in all studies. When meta-analyses were feasible, with sufficient studies to support subgroup analyses of moderator variables, we evaluated the consistency of intervention effects on QOL outcomes by elements of the prioritized intervention and integration elements. Because subgroup analyses that involve indirect comparisons (across studies) are subject to confounding, we interpreted results of these moderator analyses cautiously.

When quantitative synthesis was not feasible, we synthesized intervention effects qualitatively. We gave more weight to the evidence from higher quality studies with more precise estimates of effect. We analyzed potential reasons for inconsistency in treatment effects across studies by evaluating differences in the study population, intervention, comparator, and outcome definitions.

QUALITATIVE SYNTHESIS

After reviewing quantitative results, we used qualitative cross-case impact analysis iteratively to refine our results and develop a short list of key intervention features.[36] To carry out the analyses, we ranked studies by impact level (see below). We then analyzed the relationship of intervention and integration elements with intervention impacts using tables and graphical displays. We focused on the elements prioritized by the stakeholders and study team as key components of successful interventions. We analyzed the pattern of associations by individual elements and holistically, using the 6-level categorization of integration described previously.

Because different studies reported different outcomes using different scales, each outcome (*eg*, QOL, symptom burden) was included in only a subset of studies. To create an outcome measure applicable to all articles in the set, we developed an *impact rating scale*, an approach used previously to identify key intervention elements of collaborative care for depression.[37] To derive the impact measure, we randomly ordered the studies on a spreadsheet and listed only each study's set of outcomes, without any identifiers. We listed all the measured outcomes for each study that fell into 1 of 6 conceptual domains: QOL, symptom burden, mortality, site of death, cancer treatment at end of life, and resource utilization. Two investigators (JF, TC) considered the outcomes reported for each study and independently rated the intervention impact on a 4-point scale. Initial agreement was substantial (weighted kappa=0.4), and disagreements were resolved by discussion and consensus.

The studies were rated high, moderate, or low impact. High impact studies had to show a pattern of positive effects across all patient-centered outcomes. Moderate impact studies showed patterns of mostly positive effects across patient-centered outcomes. Low impact studies had inconsistent patterns of statistically positive and negative effects across patient-centered outcomes. All might have positive effects on end-of-life care and/or utilization. Studies deemed to have "no impact" reported all patient-centered outcomes as statistically nonsignificant. The data we used to make these determinations as well as the full definitions of the impact categories are in Appendix F.

RATING THE BODY OF EVIDENCE

The strength of evidence (SOE) for each key question was assessed using the approach described in AHRQ's Methods Guide.[38] We limited the Grading of Recommendations Assessment, Development and Evaluation (GRADE) ratings to those outcomes identified by the stakeholder and Technical Expert Panel as critical to decision making. In brief, this approach requires assessment of 4 domains: ROB, consistency, directness, and precision (Table 1).

Table 1. Strength of Evidence Required Domains

Domain	Rating	How Assessed
Quality (risk of bias)	Good Fair Poor	Assessed primarily through study design (randomized controlled trial vs observational study) and aggregate study quality
Consistency	Consistent Inconsistent Unknown/not applicable	Assessed primarily through whether effect sizes are generally on the same side of "no effect," the overall range of effect sizes, and statistical measures of heterogeneity

Domain	Rating	How Assessed
Directness	Direct Indirect	Assessed by whether the evidence involves direct comparisons or indirect comparisons through use of surrogate outcomes or use of separate bodies of evidence
Precision	Precise Imprecise	Based primarily on the size of the confidence intervals of effect estimates, the optimal information size and considerations of whether the confidence interval crossed the clinical decision threshold for using a therapy

Additional domains were used when appropriate: coherence, dose-response association, impact of plausible residual confounders, strength of association (magnitude of effect), and publication bias. These domains were considered qualitatively, and a summary rating was assigned after discussion by 2 reviewers as high, moderate, or low SOE. In some cases, high, moderate, or low ratings were impossible or imprudent to make. In these situations, a grade of insufficient was assigned. This 4-level rating scale consists of the following definitions:

- High—High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate—Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low—Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
- Insufficient—Evidence either is unavailable or does not permit estimation of an effect.

PEER REVIEW

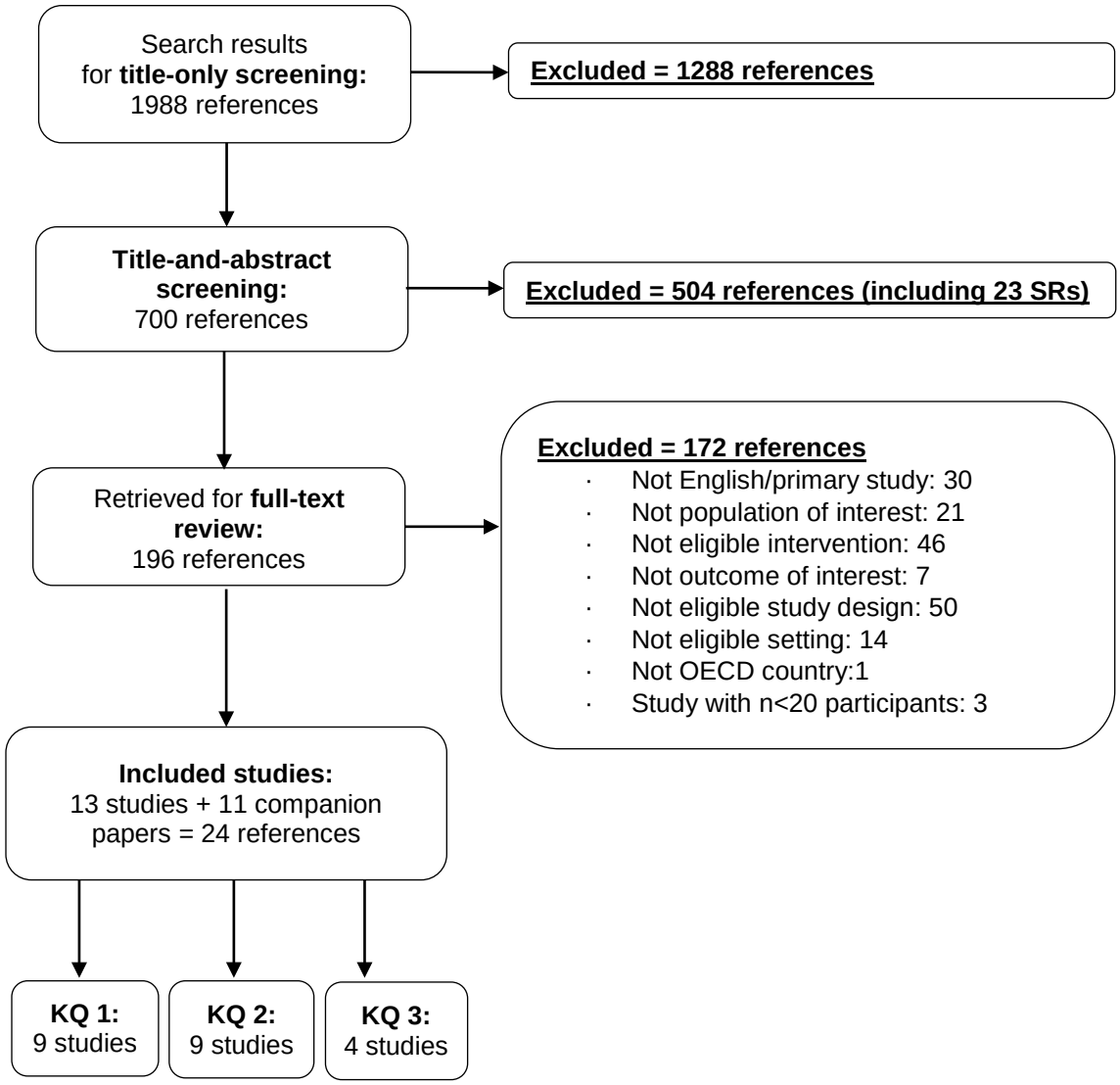
A draft version of this report was reviewed by technical experts and clinical leadership. A transcript of their comments and our responses is provided in Appendix G.

RESULTS

LITERATURE FLOW

Figure 1 shows the flow of articles through the literature search and review process. The search identified 1,916 unique citations from a combined search of MEDLINE® (via PubMed®), CINAHL and the Cochrane Central Register of Controlled Trials. An additional 72 articles were identified from manual searches of bibliographies of systematic and narrative reviews and current literature published after the search date for a total of 1,988 unique citations. After applying inclusion and exclusion criteria at the title only screening level, 700 were promoted to full abstract screening. After applying criteria at the full-abstract level, the citations were culled down to 196 articles for full-text review. Of these, 13 studies and 11 companion papers were retained for data abstraction. Appendix H presents a study characteristics table detailing all studies included in KQs 1 and 2 of this report; the results section contains a descriptive table of the KQ 3 studies.

Figure 1. Literature Flow Diagram



KEY QUESTION 1: In patients with symptomatic or advanced cancer, what are the benefits and harms of integrated outpatient palliative and oncology care compared with usual oncology care?

Key Points

- In 9 trials, integrated palliative care was delivered by multidisciplinary teams in outpatient settings, but the intensity of interventions varied considerably.
- Most studies enrolled a majority of white men and women with multiple types of advanced cancer at a median of 8 to 12 weeks following diagnosis or recurrence.
- Integrated palliative care improved short-term (SMD 0.24; 95% CI 0.13 to 0.43) but not longer-term patient QOL (SMD 0.15; 95% CI -0.12 to 0.43).
- Integrated palliative care decreased overall mortality (HR 0.77; 95% CI 0.61 to 0.98). These effects were consistent across the 4 studies reporting this outcome.
- When excluding an outlier study, overall symptom burden improved modestly, but there was no effect when evaluating all studies. Psychological symptoms did not improve with palliative care but were reported in only a subset of studies.
- Palliative care that included a specific caregiver intervention improved short-term depressive symptoms in caregivers. Caregiver experience was improved in the single trial reporting this outcome. In 3 trials, caregiver QOL was not improved.
- Utilization outcomes were inconsistently measured. Of those studies that assessed utilization, palliative care increased the likelihood of dying at home but did not reduce overall patterns of health care utilization. However, confidence intervals were wide, suggesting low statistical power.
- No studies reported on adverse events or harms of integrated palliative care in patients with advanced cancer.

Detailed Findings for KQ 1

We identified 9 trials comparing integrated outpatient palliative and oncology care to oncology care.[12,14,39-45] Most studies enrolled patients with several types of advanced cancer; the median time from diagnosis or recurrence was 8 to 12 weeks. Most studies were conducted in the United States, 2 enrolled Veterans,[12,41] and 2 used cluster-randomization.[40,42] Palliative care was compared to standard oncology care in 6 trials. Single trials compared palliative care to oncology care plus a symptom-management toolkit,[40] oncology care plus “on-demand” palliative care,[39] and delayed palliative care that began 3 months postrandomization.[41] The ROB for objective outcomes was judged low for 3 studies,[12,14,42] unclear for 3 studies,[39-41] and not applicable for the 3 studies not reporting these outcomes.[43-45] ROB for patient-reported outcomes was judged low for 2 studies,[12,45] unclear for 4 studies,[14,41,42,44] and high for the other studies. Table 2 shows the evidence profile for the 9 studies. Detailed study characteristics are reported in Appendix G.

Table 2. Evidence Profile for Integrated Palliative Care Studies (N=9)

Study designs	7 RCTs 2 cluster RCTs
Study years	2006-2017
Median number of patients enrolled (range)	207 (115-461)
Total number of patients enrolled	2,088
Mean patient age (range)	64.3 (59-67) reported in 8 studies
Median percentage female (range)	45.1% (31.5%-71.2%)
Median percentage white (range)	94.4% (84.9%-96.5%) reported in 6 studies
Number of studies with Veterans	2
Median time since diagnosis or recurrence (range)	8-12 weeks (30-60 days to 12 months)
Intervention setting	7 ambulatory 2 home
Cancer diagnoses	7 multiple cancers 1 lung cancer 1 pancreatic cancer
Patients' functional status	4 studies: ECOG 0-2 5 studies: not reported
Countries	7 USA 1 Canada 1 Europe
Risk of bias, objective outcomes	3 low 3 unclear 3 not applicable
Risk of bias, patient-reported outcomes	2 low 4 unclear 3 high

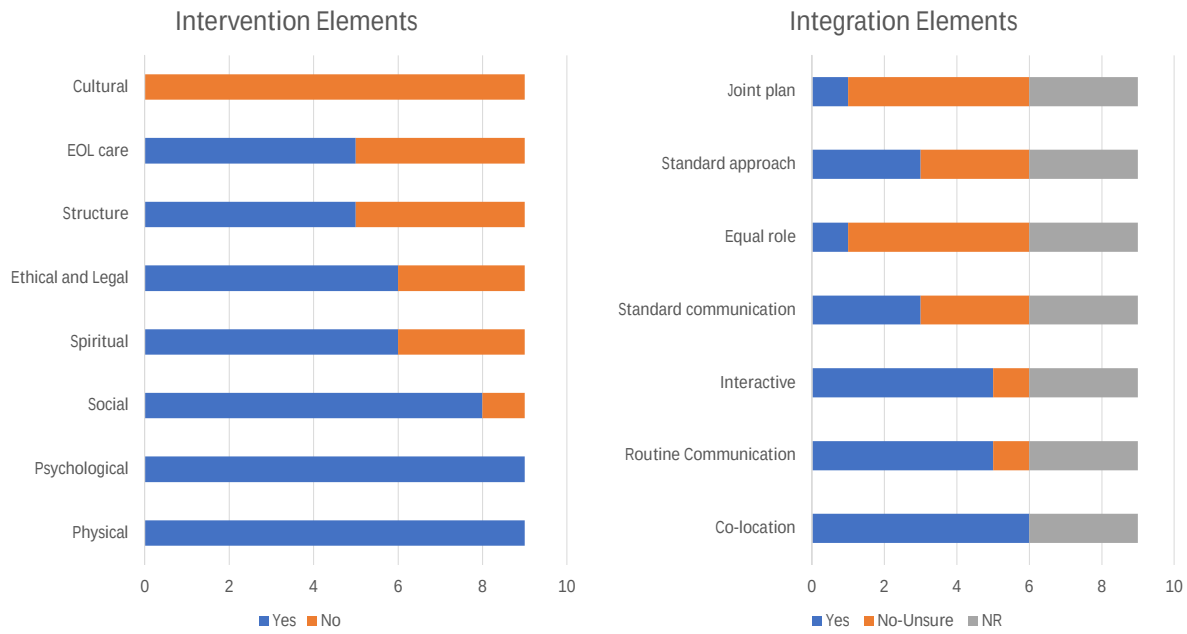
CRT=cluster-randomized trial; ECOG=Eastern Cooperative Oncology Group; RCT=randomized controlled trial

Palliative Care Interventions

All palliative care interventions in the included studies addressed physical and psychological symptoms (Appendices D and F). Most interventions also addressed social, spiritual, ethical and legal needs. End-of-life care and structural issues were addressed explicitly in half of the interventions, but cultural issues were not addressed explicitly in any studies. All but 1 study described the palliative care clinicians.[39] Palliative care services were delivered by a multidisciplinary team of 2 to 5 clinicians; all included nurses, 5 included a palliative care physician, 3 included a mental health professional (medical social worker, psychologist, or licensed clinical social worker and psychiatrist or psychologist), and 2 included chaplains. All studies provided services during outpatient visits; 4 also included telephone-based care, and 3 described delivery of written materials. One study used telephone as the primary method of intervention delivery.[12] Palliative care services were delivered for a median of 17 weeks in studies with a specified duration; 3 studies continued the intervention until death with a maximum follow-up of 4 years. The intensity of services varied greatly, ranging from 4 sessions weekly[12] to contacts every 2 to 4 weeks until death.[39]

Integration between palliative care and oncology services was rarely described, but 6 of the 9 authors responded to our request for information. In all trials for which the authors responded, palliative care services were colocated in the same facility with oncology services. Standard communication about specific treatment issues, interactive communication, and routine communication exchanges between palliative care and oncology clinicians were reported in at least half the studies (Figure 2). Integration elements of the palliative care interventions are described in more detail in KQ 2.

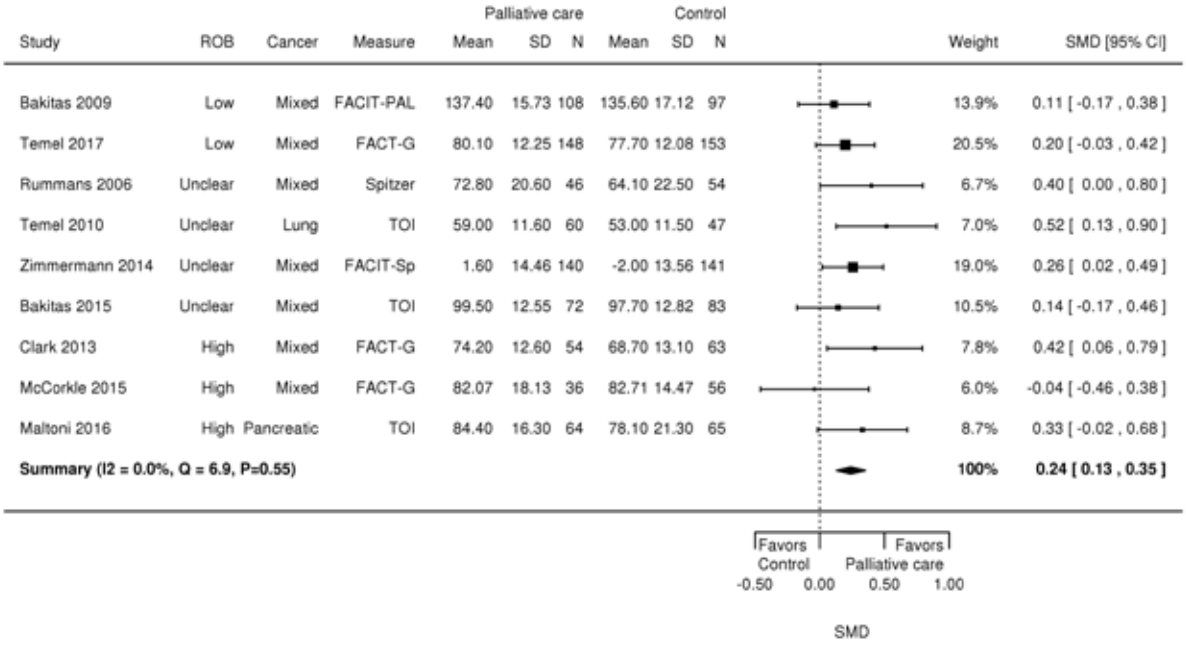
Figure 2. Clinical Domains and Integration Elements of the Interventions



Effects on Functional Status, Overall Symptom Burden, and Psychological Symptoms

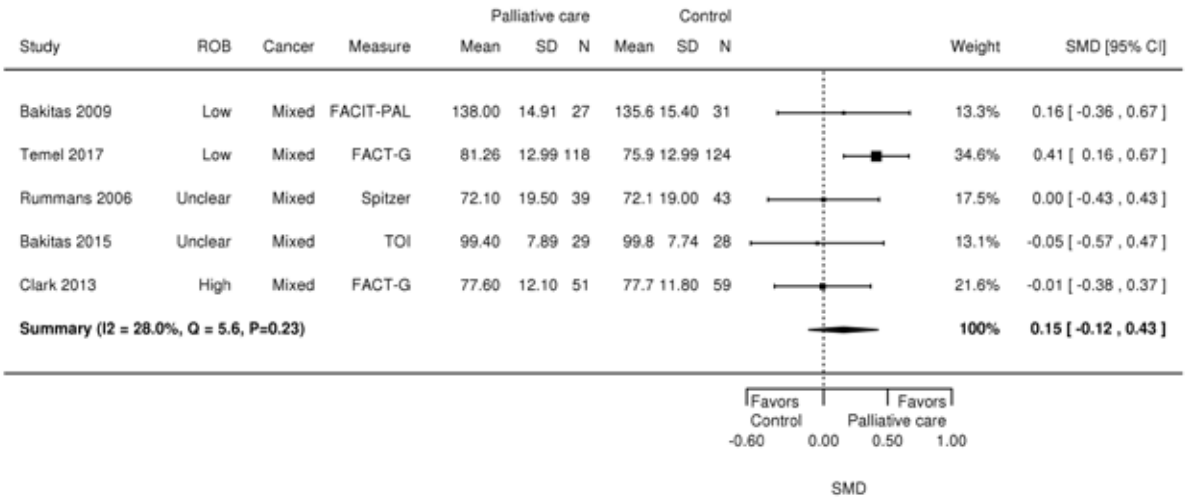
All studies reported short-term (1-3 months) effects of integrated palliative care on QOL. Integrated palliative care improved QOL (SMD 0.24; 95% CI 0.13 to 0.35; I^2=0%; Q=6.9; p=0.55) (Figure 3). Positive effects were consistent, ranging from small to moderate benefit in all but 1 study. In the 6 studies reporting longer-term effects at 6-12 months, QOL was not improved (SMD 0.15; 95% CI -0.12 to 0.43; I^2=28%; Q=5.6; p=0.23), with estimates from individual studies clustering around no effect (Figure 4). One study found an interaction effect, showing greater effects of palliative care for patients with lung cancer than those with gastrointestinal cancer.[45] Of note, longer-term QOL was not a primary study endpoint in any of these studies, and study dropout due to death and disease progression likely limited the ability to detect longer-term differences in outcomes. Additionally, it might be expected that longer-term QOL would be expected to decrease as symptom burden increases and end of life nears.

Figure 3. Short-term (1-3 months) Effects of Integrated Palliative Care on QOL



Abbreviations: CI=confidence interval; FACIT-PAL=Functional Assessment of Chronic Illness Therapy-Palliative Care; FACIT-Sp=Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being; FACT-G=Functional Assessment of Cancer Therapy-General; FACT-Hep=Functional Assessment of Cancer Therapy-Hepatobiliary; N=study sample size; QOL=quality of life; ROB=risk of bias; SD=standard deviation; SMD=standardized mean difference; TOI=Trial Outcome Index

Figure 4. Long-term (6-12 months) Effects of Integrated Palliative Care on QOL

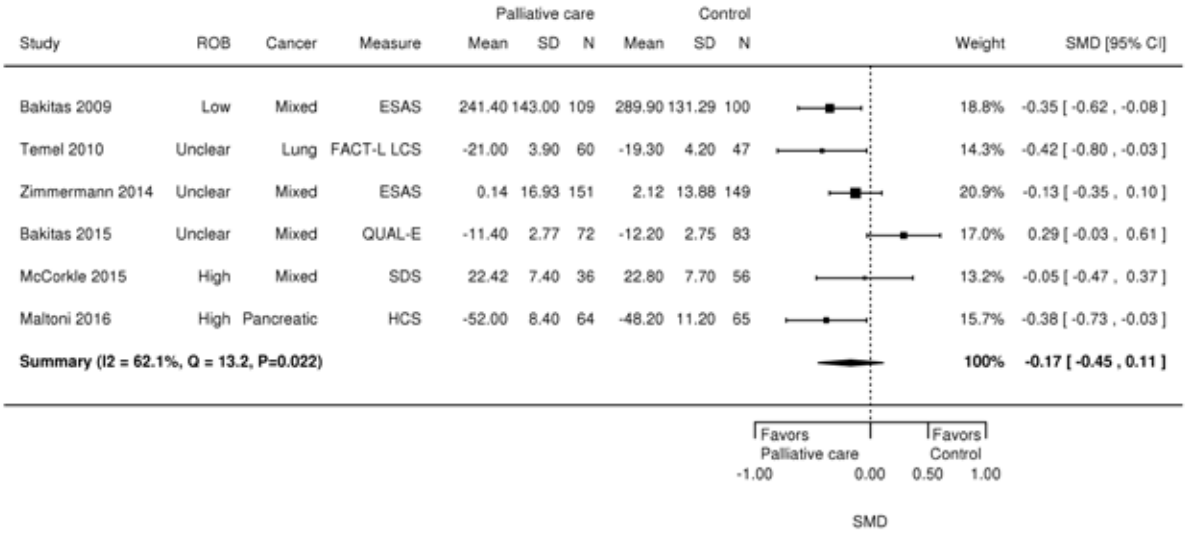


Abbreviations: CI=confidence interval; FACIT-PAL=Functional Assessment of Chronic Illness Therapy-Palliative Care; FACIT-Sp=Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being; FACT-G=Functional Assessment of Cancer Therapy-General; FACT-Hep=Functional Assessment of Cancer Therapy-Hepatobiliary; N=study sample size; ROB=risk of bias; QOL=quality of life; SD=standard deviation; SMD=standardized mean difference; TOI=Trial Outcome Index

Effects of integrated palliative care on overall symptom burden were reported in 6 studies (Figure 5). At 1 to 3 months postrandomization, patients assigned to integrated palliative care showed small but statistically nonsignificant improvements in symptom burden (SMD -0.17; 95% CI -0.45 to 0.11; I^2=62%; Q=13.2; p=0.022). A seventh study[44] only reported effects on symptom burden as statistically nonsignificant and so could not be included in the meta-analysis; omitting this study from the meta-analysis may bias the estimate of effect.

All but one study[41] showed small-to-moderate improvement in symptom burden. This outlier study, judged unclear ROB, was conducted in 3 settings, including a VA medical center, and did not include longitudinal in-person visits with specialist palliative care clinicians. After an in-person consultation by a board-certified palliative care clinician, an advanced practice nurse delivered structured coaching sessions by telephone, with 3 sessions that included attention to symptom management. A sensitivity analysis that excludes this study shows a consistent pattern of decreased symptom burden with integrated palliative care (SMD -0.25; 95% CI -0.39 to -0.11; I^2=0%; Q=3.8; p=0.43).

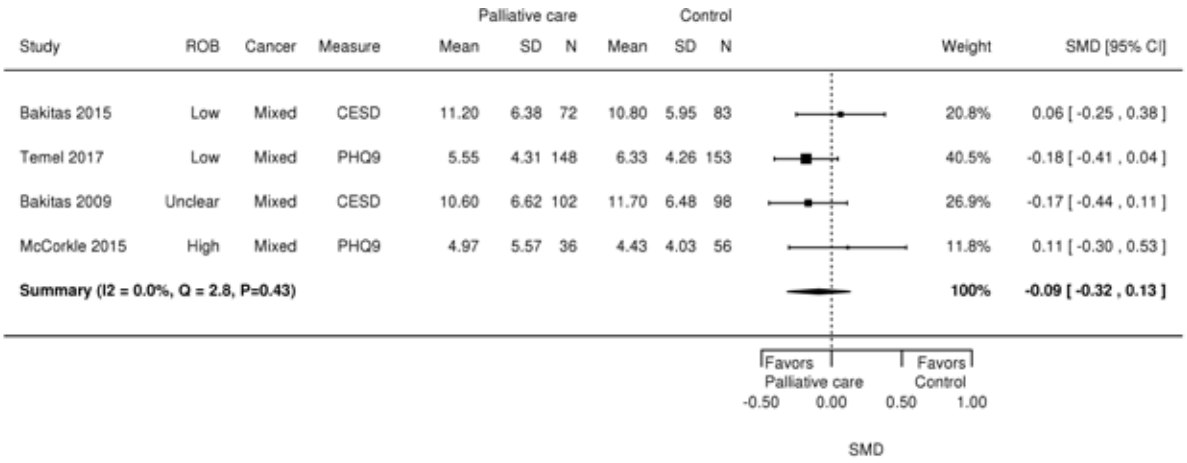
Figure 5. Effects of Integrated Palliative Care on Overall Symptom Burden



Abbreviations: CI=confidence interval; ESAS=Edmonton Symptom Assessment Scale; FACT-L=Functional Assessment of Cancer Therapy-Lung; HCS: Hepatobiliary Cancer Subscale; LCS=Lung cancer subscale; N=study sample size; QUAL-E= Quality of life at end of life symptom impact subscale; ROB=risk of bias; SD=standard deviation; SDS=Symptom Distress Scale; SMD=standardized mean difference

Effects of integrated palliative care on one or more psychological symptoms were reported in all but 1 study.[42] Six studies reported the effects on depression symptoms.[12,14,39-41,45] There was no short-term effect of the intervention on depressive symptoms in the 4 studies reporting severity as a continuous outcome (SMD -0.09; 95% CI -0.32 to 0.13; Q=2.8; p=0.43, I^2=0%) (Figure 6). One[14] of 2 studies[14,39] reporting the proportion meeting the threshold for depressed mood showed an intervention effect (n=104; 4% vs 17% meeting criteria for major depression; p=0.04).

Figure 6. Effects of Integrated Palliative Care on Depressive Symptoms



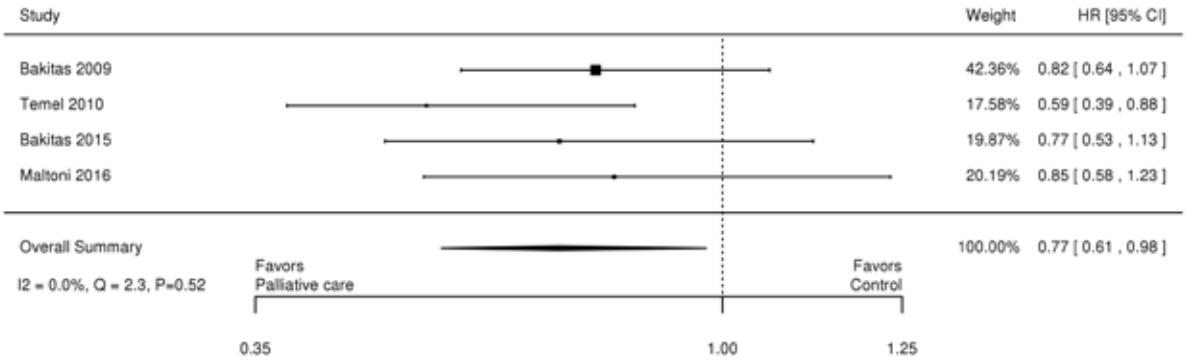
Abbreviations: CES-D=Center for Epidemiologic Studies Depression Scale; CI=confidence interval; PC=palliative care; PHQ=Patient Health Questionnaire; N=study sample size; ROB=risk of bias; SD=standard deviation; SMD=standardized mean difference

Two studies[14,39] reported the proportion of patients with significant anxiety symptoms; neither showed a difference between the palliative care and oncology care groups. Two studies[43,44] reported effects on transient mood states using the Profile of Mood States, which assesses tension or anxiety, anger or hostility, vigor or activity, fatigue or inertia, depression or dejection, and confusion or bewilderment. Neither study showed a statistically significant effect. In summary, there was no consistent pattern of beneficial effects on psychological symptoms.

Effects on Survival

Four studies reported effects on overall mortality.[12,14,39,41] Overall mortality was reported at 12 months in 2 studies,[39,41] a mean of 14.6 months in 1 study,[12] and at 4.5 to 36 months follow-up in another.[14] We used hazard ratios reported by the study or estimated hazard ratios from reported data. Two studies were judged low ROB[12,14] and 2 were unclear ROB for this outcome. All studies compared integrated palliative care to usual oncology care except for Bakitas et al (2015), in which the control patients began delayed palliative care 3 months postrandomization. Integrated palliative care was associated with lower all-cause mortality (HR 0.77; 95% CI 0.61 to 0.98; I^2=0%; Q=2.3; p=0.52) (Figure 7).

Figure 7. Effects of Integrated Palliative Care on All-Cause Mortality

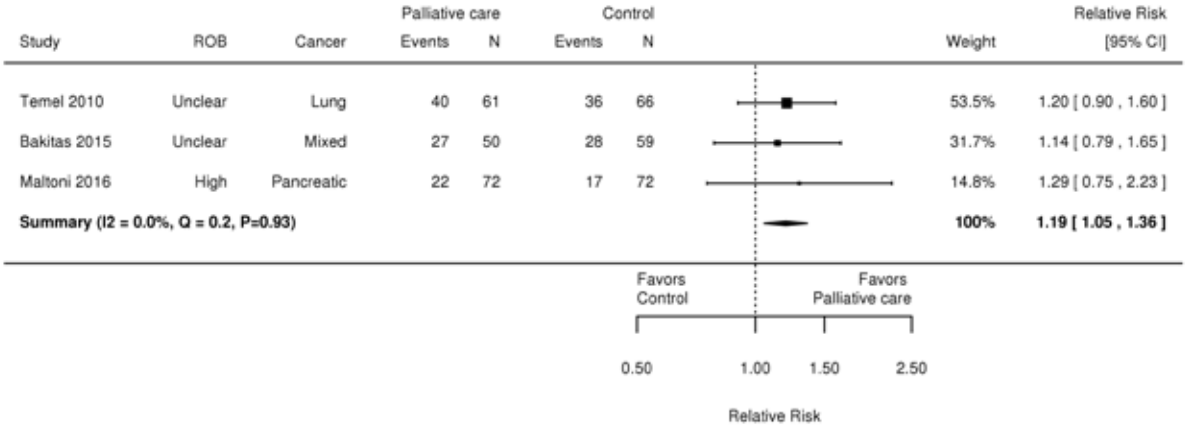


Abbreviations: CI=confidence interval; HR=hazard ratio

Effects on End-of-Life Care

Death at home was reported in 3 trials (567 patients) with follow-up ranging from 6 to 35 months.[14,39,41] Patients who received palliative care were more likely to die at home (RR 1.19; 95% CI 1.05 to 1.36; I^2=0%; Q=0.2; p=0.93) (Figure 8). Effects on site of death were consistent across studies.

Figure 8. Risk of Dying at Home with Palliative Care



Abbreviations: CI=confidence interval; SD=standard deviation; SMD=standardized mean difference

Aggressiveness of care near the end of life was reported in 3 trials,[14,41,42] but measures varied greatly. Thus, we synthesized these results qualitatively. One study judged low ROB[14] that was conducted in patients with lung cancer reported a composite measure, which was considered met for any patient who had at least 1 of the following: chemotherapy 14 days before death, no use of hospice care, or admission to hospice 3 days or less before death. Palliative care patients were less likely than those assigned to usual oncology care to receive aggressive end-of-life care on this composite outcome (33% vs 54%; p=0.05). Three studies judged low ROB reported chemotherapy use at end of life,[14,41,42] only 1 of which showed an intervention effect (chemotherapy in the last 60 days of life, 32/61 vs 47/67; p=0.05).[14] One study reported on the proportion of patients receiving chemotherapy at all,[42] while the other reported receipt of chemotherapy in the last 60 days of life[41]; neither showed an intervention effect. Only 1 study reported the proportion of patients receiving radiotherapy[42]; there was no intervention effect. In summary, intervention effects on end-of-life care were inconsistent. While the interventions consistently had an impact on the likelihood of dying at home, most studies did not report measures of aggressiveness in care at the end of life; among those that did, only 1 study showed an intervention effect.

Effects on Health Care Utilization

Measures of utilization were not reported in all trials, and when present were not reported consistently across studies. Thus, we synthesized these results qualitatively. Emergency department use was reported in 4 of 6 trials.[12,14,39,41] No intervention effects were noted in any study, but in the 3 studies reporting the proportion of patients with an emergency department visit, visits were modestly lower (risk ratio range 0.73 to 0.93). Hospitalization data were also reported in these 4 studies, with no apparent intervention effect.[12,14,39,41] Again, hospitalization rates were modestly lower (risk ratio range: 0.73 to 0.96) in the 3 studies reporting this rate. For both emergency department visits and hospitalizations, the estimates of effect were imprecise and do not exclude a clinically important effect. Only 2 studies reported intensive care unit utilization[12,41]; there was no apparent intervention effect.

Costs of care were reported in only 1 study of patients with lung cancer.[14] The intervention was associated with a lower mean total cost per day throughout the entire study period, but this

difference was not statistically significant ($117; p=0.13). Costs for the provision of chemotherapy in the last 30 days of life were significantly different, with the intervention yielding a $757 mean reduction compared to the standard care arm (p=0.03). In summary, only a minority of trials reported utilization data, and measures were inconsistent and not planned primary outcome measures in any studies. While these limited data do not demonstrate an intervention effect, studies do not appear to be powered to detect small-to-moderate effects on utilization.

Effects on Other Outcomes

Caregiver experience was reported in 3 trials (2 companions).[41-43,46,47] The best data come from a cluster-randomized trial judged unclear ROB that enrolled 461 patients with advanced cancers, and reported caregiver experience using a measure that assessed satisfaction with information-giving, availability of care, psychological care, and physical care (range 16-80 with higher scores better).[42] Only 182 caregivers participated due to unavailability of caregivers, declining to participate, or not completing baseline measures. The intervention involved a consultation and follow-up in the oncology palliative care clinic by a palliative care physician and nurse. Visits occurred monthly and were supplemented by telephone support as needed. For patients assigned to palliative care, caregiver experience was better at 3 months (mean change 1.4 vs -3.1; p=0.007; SMD 0.39; 95% CI 0.02 to 0.77, calculated by review authors) and 4 months (mean change 0.6 vs -2.4; p=0.02; SMD 0.27; 95% CI -0.10 to 0.65, calculated by review authors). Caregiver quality of life did not differ between groups. Two other trials (1 companion)[41,43,47] reported on caregiver quality of life, which may be related to (but does not directly measure) caregiver experience. Both trials used the Quality of Life Index-Cancer Scale, a 35-item self-report measure assessing physical, emotional, spiritual, and family dimensions of well-being. Palliative care was delivered by a multidisciplinary team and was designed to address multiple domains of QOL. One study incorporated a telephone-based intervention for caregivers addressing multiple topics such as the role of the caregiver, problem-solving, self-care, effective partnering, building a support team, decision support, and advance care planning. There were no intervention effects in either study at 3 months[41,47] or 27 weeks.[43] Collectively, 3 trials showed no benefit of integrated palliative care on caregiver QOL.

A single study (1 companion) reported effects of palliative care on caregiver depressive symptoms and caregiver burden.[41,48] Caregivers were enrolled for about 60% of the participating patients. Outcomes were assessed at 3 months, at which time the comparison group was eligible for palliative care and in the subset where the care recipient died, at 8 to 12 weeks after death. At 3 months postrandomization, depressive symptoms were lower (mean difference -3.4 on the Center for Epidemiological Studies Depression Scale, standard error 1.5; Cohen's d -0.32; p=0.02) for caregivers randomized to early palliative care. Of the 70 caregivers eligible for post-death assessment, 44 (63%) responded. There was no effect on depressive symptoms (Cohen's d 0.07; p=0.88) or grief (Cohen's d -0.21; p=0.51). Caregiver burden was measured with the 14-item Montgomery-Borgatta Caregiver Burden Scale, which included objective, demand, and stress burden subscales. At 3 months, there were no intervention effects on any of the 3 caregiver burden subscales (Cohen's d -0.01 to 0.09; p≥0.29). In an analysis confined to caregivers whose care recipient had died, stress burden (Cohen's d -0.44; p=0.01), but not demand or objective burden, was lower in caregivers assigned to early palliative care.

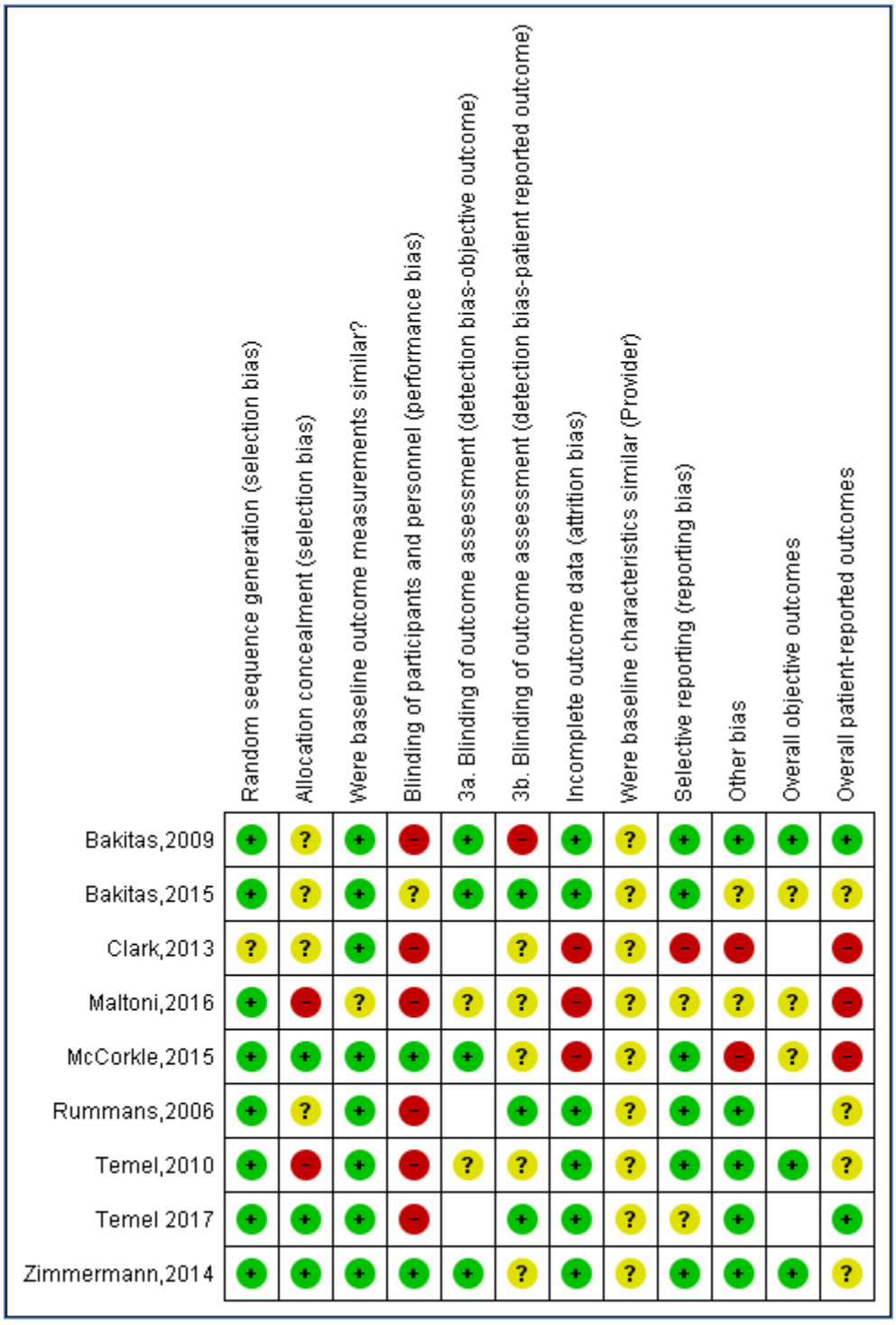
Patient experience was reported in the cluster-randomized trial, using the same multidimensional measure completed by caregivers.[42] For patients assigned to palliative care, patient experience was better at 3 months (mean difference 3.8, 95% CI 1.74 to 5.85; Cohen's d 0.47). These benefits were greater at 4 months (mean difference 6.0, 95% CI 3.94 to 8.05; Cohen's d 0.73).

Adverse effects of integrated palliative care were not specified as an outcome and were not reported in any trials.

Quality of Evidence for KQ 1

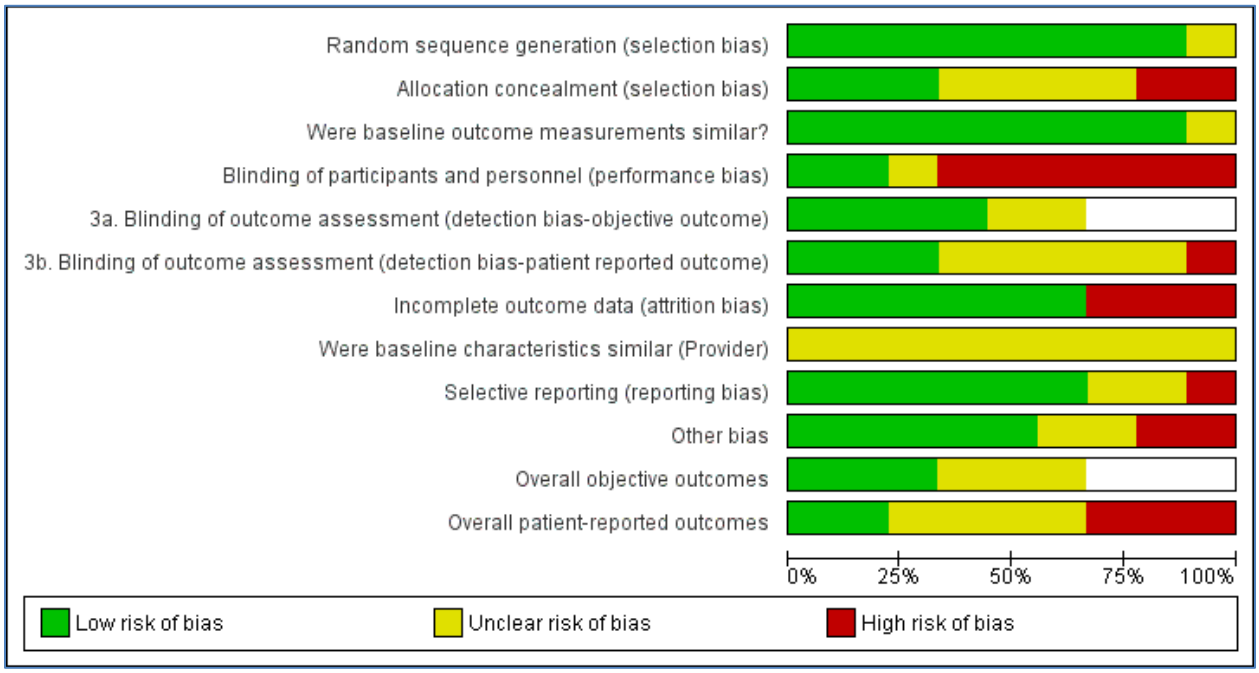
The ROB for objective outcomes was judged low for 3 studies,[12,14,42] unclear for 3 studies,[39-41] and not applicable for the other 3 studies (Figures 9 and 10). ROB for patient-reported outcomes was judged low for 2 studies,[12,45] unclear for 4 studies,[14,41,42,44] and high for the other studies. Patterns that led to judgments of higher ROB included (1) inadequate or unclear allocation concealment (n=6), (2) outcome assessments that did not clearly blind to intervention assignment (n=6), and (3) incomplete outcome data (n=3). Cluster-randomization by oncology specialty (*eg*, lung vs gastrointestinal malignancy)[40] also could have affected results. If palliative care has differential effects by cancer diagnoses, then this randomization strategy would confound results. Another factor may be the comparator: 1 study used "on-demand" palliative care in the control arm but did not report how often these services were delivered.[39] Another study used delayed palliative care as the comparator,[41] which would serve to narrow intervention effects on palliative care services that were offered to the control arm.

Figure 9. Risk of Bias Ratings for Each Study[a]



[a] Empty cells indicate items that were not applicable.

Figure 10. Summary Ratings Across Studies for Each ROB Domain[a]



[a] White space indicates items that were not applicable.

KEY QUESTION 2: Which features of integrated palliative and oncology care are associated with greater benefit to patients with symptomatic or advanced cancer?

Key Points

- Published trials of palliative care do not routinely describe elements of integration with oncology care. Classifying integration required author queries for additional data.
- Of 9 trials, 2 were classified as having basic collaboration onsite and 4 as having close collaboration onsite with some systems integration. Three studies could not be classified due to missing information.
- We did not identify an association between integration level and overall intervention effects or effects on short-term quality of life. However, these analyses were limited by the small number of studies and the limited range of integration levels.

Detailed Findings for KQ 2

We used the Integrated Practice Assessment Tool (IPAT)[19] to classify the level of collaboration and integration for each trial. The IPAT identifies 6 levels of collaboration and integration. The key element of integration for Levels 1 and 2 is communication, with the distinction between Level 1 and Level 2 being the frequency and type of communication. Physical proximity is the key element for Levels 3 and 4, with Level 4 requiring some degree of shared systems. The key element of Levels 5 and 6 is practice change, with the highest level being characterized by a joint patient treatment plan, balanced and shared resources, equal roles in patient care, and providers being involved in care in a standard way across all patients. After classifying the level of

integration for a trial, we used quantitative and qualitative approaches to examining associations between integration and intervention effects.

Levels of Integration

Elements of integration were rarely described in the publications, and available data on integration elements was based primarily on retrospective report from authors. Data on integration were supplied by authors from 6 of the 9 trials.[12,14,40-42,45] Using these data, the IPAT decision tree model was used to cascade each trial to a specific level of integrated health care (Table 3). The level of integration showed little variability across studies. Two trials[12,42] were classified Level 3 Integration (Basic Collaboration Onsite), and 4 studies [14,40,41,45] were classified Level 4 integration (Close Collaboration Onsite with Some Systems Integration). Palliative care and oncology teams were physically or virtually located at the *same facility* across all trials—but not necessarily colocated in the same clinical space. Authors of all trials endorsed exchanging information between palliative care and oncology teams as a standard and routine practice, and all but 1 trial involved routine exchange of written or electronic information.[14] With the exception of one trial,[41] all trials involved bidirectional, interactive communication between palliative care and oncology teams. Palliative care and oncology teams were involved in care in a standard way across all providers and patients in only 3 trials,[40,41,45] all of which were the most recently published trials. Palliative care and oncology teams had equal roles in decision making in only 1 trial,[14] and only 1 trial involved a joint treatment plan for patients.[41]

Table 3. Levels of Integration and Impact Ratings for Integrated Palliative and Oncology Care

Study[a]	Integration Elements							Level of integration Impact rating[b]
	Care teams colocated?	**Written or electronic information exchanged routinely?**	**Care teams communication bidirectional?**	**Information exchanged as standard and routine practice?**	**Care providers have equal roles in decision making?**	**Care standardized across ALL patients?**	**One joint treatment plan for cancer patients?**	
Bakitas, 2009[12]	Yes	Yes	Yes	Yes	No	No	No	Level 3 Moderate
Bakitas, 2015[41]	Yes	Yes	Unsure	Yes	No	Yes	Yes	Level 4 Low
Clark, 2013[43]	No author response							Unclear Low
Maltoni, 2016[39]	No author response							Unclear Low
McCorkle, 2015[40]	Yes	Yes	Yes	Yes	No	Yes	No	Level 4 None
Rummans, 2006[44]	No author response							Unclear Low
Temel, 2010[14]	Yes	No	Yes	Yes	Yes	No	No	Level 4 Moderate
Temel, 2017[45]	Yes	Yes	Yes	Yes	Unsure	Yes	No	Level 4 Low
Zimmermann, 2014[42]	Yes	Yes	Yes	Yes	No	No	No	Level 3 Low

[a] Answers were solicited from the first author of each article. Report investigators also answered questions based on reading the published article; however, with only 1 exception, the report investigators' answer was always unsure.

[b] Impact ratings range from none to high and are independently derived based on a judgment about intervention effects (*eg*, effect size or statistical significance) across 6 outcome domains.

Association Between Integration Classes, Intervention Elements, and Intervention Effects

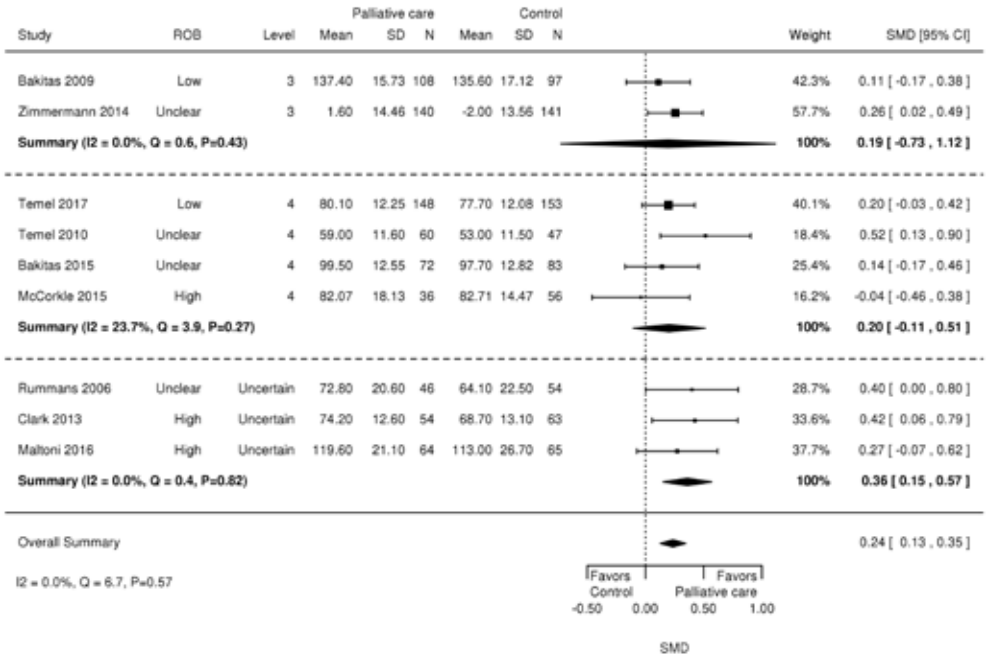
Impact ratings were assigned after considering intervention effects on 6 outcome categories. Six trials[39,41-45] were classified as "low impact," 2 trials[12,14] as "moderate impact," and 1 trial as "no impact."[40] The limited number of studies, and the limited variability in integration levels and impact ratings, precluded quantitative analyses to examine the association between integration levels and intervention impact. Qualitative analysis of this association identified no consistent pattern of results. Trials with Level 4 integration ratings had impact ratings of low,[41,45] moderate,[14] and none.[40] The 2 trials with Level 3 integration ratings[12,42] included all of the same elements of integration but had different impact ratings (moderate and low, respectively).

All trials included 3 of the elements of integration: colocation, standard and routine information exchange, and routine exchange of written or electronic information. These integration elements did not appear to be associated with a greater benefit for patients given that impact ratings ranged from none to moderate across the 6 trials. Authors of the studies were asked about integration elements with a "yes/no/unsure" response option. Thus, specific information about communication and colocation was not available, and it is possible that degree of physical proximity and frequency and method of information exchange was diverse and could account for some variability in the impact ratings.

Three of the 7 elements measured (*ie,* equal roles in decision making; providers involved in care in a standard way across all patients; having one joint patient treatment plan) are among the required elements for Integration Levels 5 (Close Collaboration Approaching an Integrated Practice) and 6 (Full Collaboration in a Transformed/Merged Integrated Practice). Only one of these 3 elements was related to a higher impact rating. Specifically, one trial[14] involved equal roles in decision-making among palliative care and oncology providers and had a moderate impact rating. In contrast, when all other elements of communication and colocation were equal across trials, those trials that included standardized care across all patients, 1 joint patient treatment plan, or both, had impact ratings of no[40] or low.[40-42,45] Further, 1 trial[12] that included none of these higher-level integration elements had a moderate impact rating. These results may suggest that palliative care and oncology teams that have interactive, routine, and written or electronic communication and some degree of colocation more greatly benefit patients with cancer than teams that additionally have 1 joint patient treatment plan and a standard approach to care across all patients.

Among the 6 trials for which there were data on level of integration, the relation between integration level and effects of the intervention on short-term QOL (1-3 months) was examined quantitatively (Figure 11). Quantitative analysis was possible for this outcome, specified *a priori* as a primary outcome, because it was reported in all trials. Overall, there was no association between level of integration and intervention effects on short-term QOL. Two of the 6 studies[14,42] had a significant positive effect on short-term QOL, and both studies included the following 3 elements of integration: (1) interactive, bidirectional communication, (2) standard and routine information exchange, and (3) colocation.

Figure 11. Integration Category and Effects on Short-term QOL



Abbreviations: CI=confidence interval; N=study sample size; QOL=quality of life; ROB=risk of bias; SD=standard deviation

In addition to elements of integration, we assessed the association between palliative care intervention elements (the 8 domains of structure, physical, psychological, social, spiritual, cultural, end of life, ethical/legal[29]) and the overall impact of the intervention (Table 4). No clear pattern of association between palliative care domains and impact ratings emerged. All trial interventions involved physical (*ie*, interdisciplinary assessment and management of pain and other physical symptom needs) and psychological (*ie*, psychological and psychiatric assessment and treatment of patient-family and staff needs including grief and bereavement services) aspects of palliative care as this was a requirement for inclusion in the review. All trials except one[39] involved the social aspects of palliative care (*ie*, person-centered interdisciplinary assessment to identify and promote the patient-family strengths, needs, and goals). None of the study interventions described cultural aspects of palliative care (*ie*, assessment of patient-family cultural needs and service in a culturally and linguistically appropriate manner). The 2 studies with the highest impact ratings[12,14] both included end-of-life (*ie*, interdisciplinary team attends to patient-family values, preferences, beliefs, culture, and religion to promote a peaceful and dignified death and post-death plan for support) and ethical/legal (*ie*, plan of care based on patient-surrogate goals preferences, and choices are respected within the limits of applicable state and federal law) aspects of care. One of these studies[14] included structural processes (*ie*, involvement of a specialty-trained palliative care interdisciplinary team striving for best practices inclusive of quality assessment and performance improvement) and spiritual (*ie*, interdisciplinary assessment and respectful attention to patient-family religious, spiritual, or cultural practices before, at, and after death) aspects of care while the other did not.[12] Overall, trials that included more aspects of palliative care than others did not appear to have higher impact ratings. Similarly, no constellations of specific aspects of palliative care were found to relate to impact ratings in a meaningful way.

Table 4. Palliative Care Intervention Domains and Impact Ratings

Study	Structural	Physical	Psychological	Social	Spiritual	Cultural	End of Life	Ethical/Legal	Impact Rating[a]
Bakitas, 2009[12]	No	Yes	Yes	Yes	No	No	Yes	Yes	Moderate
Bakitas, 2015[41]	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Low
Clark, 2013[43]	No	Yes	Yes	Yes	Yes	No	No	Yes	Low
Maltoni, 2016[39]	Yes	Yes	Yes	No	Yes	No	No	No	Low
McCorkle, 2015[40]	Yes	Yes	Yes	Yes	No	No	No	Yes	None
Rummans, 2006[44]	No	Yes	Yes	Yes	Yes	No	Yes	No	Low
Temel, 2010[14]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Moderate
Temel, 2017[45]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Low
Zimmermann, 2014[42]	Yes	Yes	Yes	Yes	No	No	No	No	Low

[a] Impact ratings range from none to high and are independently derived based on a judgment about intervention effects (*eg*, effect size or statistical significance) across 6 outcome domains.

Quality of Evidence for KQ 2

Elements of integration were rarely described in the manuscripts, and all authors were contacted to obtain information about the degree to which trials included the 7 elements of integration measured in this review. Six authors responded with information; however, authors were reporting retrospectively and were, in some cases, unsure about details of the studies (some of which were conducted nearly a decade ago). Thus, the nature of integration element measurement impacts the validity and quality of the data.

KEY QUESTION 3: What are the most common and important barriers to implementing integrated palliative and oncology care in Veterans Affairs settings?

Key Points

- Few studies directly addressed common and important barriers to implementing integrated palliative and oncological care in the VHA.
- Common barriers to implementation included low participation rates to shared appointments, perceptions that palliative care is meant to be used later in the disease trajectory, and poor communication and coordination among providers and patients.
- Facilitators to implementation included greater collaboration among local leaders within a health care system, improved patient-centered care, and patient-provider education about roles and responsibilities of care both in oncology and palliative care services.

Detailed Findings for KQ 3

We identified 4 studies[49-52] addressing barriers to integrated palliative care in VA. However, only 1 study was designed specifically to address this objective.[50] The study designs included qualitative, mixed-methods, and retrospective chart review; 3 of the studies enrolled Veterans and 1 study enrolled health care providers and health system leaders from the VHA. All studies were conducted in the United States (Table 5). Detailed study characteristics are reported in Table 6. The ROB was judged low for all studies.[49-52]

Table 5. Study Characteristics for KQ 3 Studies

Study	Design	Study Population	Intervention and Comparator	Total N	Mean Age	% Female	Setting
Bakitas, 2016[49]	Mixed-methods summative evaluation	Advanced solid tumor or hematological malignancy (prognosis 6-24 months) who were recently diagnosed and caregivers defined as "someone who knows you well and is involved in your medical care"	N=57; early palliative care telehealth (6 weekly sessions) using a patient decision aid N=20 caregivers (3 weekly sessions)	77	64 (10.4)	63% N=52	National Cancer Institute-designated cancer center, VA medical center, and outreach clinics
Bekelman, 2016[50]	Cross-sectional; qualitative semi-structured interviews	Health care providers and local, regional, and national health system leaders from the VHA	NA	17	NR	NR	VHA
Maloney, 2013[51]	Qualitative descriptive study RCT; in-depth, semi-structured interviews	Newly diagnosed advanced or recurrent lung, gastrointestinal, genitourinary, or breast cancer	N=27; original study included multicomponent psychoeducational intervention N=26; usual care	N=53 (1 participant interview was lost due to technical difficulties)	63.3 (11.1)	52.8% N=28	VA hospital outpatient clinic
Sharma, 2016[52]	Retrospective chart review	Veterans with advanced cancer who died between 2002 and 2009	N/A	N=567 ≥ Age 65=372 Age 40-64=195	≥ Age 65=75.8 (6.69) Age 40-46=57.7 (4.76)	≥Age 65=3.8% N=14 Age 40-46= 4.1% N=8	VA medical center

Patient Perspectives of Palliative Care Services

One study investigated the benefits and burdens of a palliative care intervention implemented at time of the diagnosis in 53 Veterans.[51] Using qualitative thematic analysis, 4 themes emerged regarding the benefits of the palliative care intervention: (1) enhanced problem-solving, (2) better coping, (3) feeling empowered in health care choices and dealing with friends and family, and (4) feeling supported, reassured, and hopeful. Barriers to trial participation were completing questionnaires and being reminded about illness by participation. Barriers relevant to implementing palliative care were lack of attendance by other participants to shared medical appointments and the perception that the palliative care intervention did not apply until later in the diagnosis.

Utilization of Palliative Care

Utilization of palliative care in Veterans who died of advanced cancer was assessed in 1 retrospective study.[52] Utilization of palliative care services was defined as the mean number of days of referral to hospice before death, and mean length of stay in hospice before death. Utilization of acute care services was defined as a composite outcome of emergency room visits, hospital admission, and intensive care unit (ICU) admission. Older Veterans (≥65 years of age; n=372) were referred to palliative care earlier than younger Veterans (40-65 years of age; n=195) (47.3 vs 34.5 days, p=0.015), and older Veterans spent more time in hospice (32.5 vs 20.2 days, p=0.007). There was no difference found between older and younger Veterans who declined PC. Older Veterans had fewer hospital admissions (p=0.043) and ICU admissions (p=0.030). During the last month of life, the odds of having at least one emergency room visit, hospital admission, or ICU visit did not differ between younger and older Veterans.

Utilization of Patient Decision Aid in Palliative Care

One mixed-method study judged at low ROB[49] assessed the utilization of the commercial decision aid "Looking Ahead: Choices for Medical Care When You're Seriously Ill" (Health Dialog Services Corporation, 2007) in 57 patients and 20 caregivers participating in an RCT of early palliative care.[41] The patient decision aid included a 60-page booklet and 37-minute video. The majority of patients (93%) and all caregivers recommended the patient decision aid. Ninety-three percent of patients and 95% of caregivers watched the video. Forty-six percent of patients read all or most of the book. Seventy-two percent of the patients recommended that the program be received at time of diagnosis, while 14% recommend prior to diagnosis and 14% recommended when treatment is no longer working. Three themes emerged regarding patient-reported impact of the patient aid: (1) feeling empowered and informed to question health care providers, (2) becoming aware of different options (such as palliative care and hospice care), and (3) engaging in advance care planning and recognizing the importance of including family members in decisions.

Organizational Barriers and Facilitators to Implementing Outpatient Palliative Care

Organizational factors related to implementing outpatient palliative care services in VA was assessed in one study.[50] In a cross-sectional qualitative study, 17 VA health care providers from multiple clinical disciplines and health care leaders including chiefs of service, regional, and national leaders, completed semi-structured interviews. The domains of the Consolidated Framework for Implementation Science[53] were used to identify barriers and facilitators to implementing outpatient palliative care. Five themes related to barriers and facilitators of

implementation emerged: (1) develop performance measures for patient-centered care and outcomes that can be used to measure the quality and incentivize the spread of outpatient palliative care, (2) justify additional personnel cost and assess and address practical issues such as staffing and space prior to implementation, (3) communication and coordination with other providers and coordination should be tailored to local and individual preferences, (4) collaborate with local leaders to determine how outpatient palliative care aligns with local programs and needs, and (5) clarify the roles and responsibilities of outpatient palliative care versus primary and specialty care for disease management in advanced chronic illness, and structure core components of outpatient palliative care to allow for flexibility during implementation.

Summary

This review yielded a small number of eligible studies to answer KQ 3. Overall, barriers to implementing integrated palliative and oncological care in the VHA potentially include age, shared medical appointment format, timing of palliative care services (some patients early in the illness may not be ready), lack of performance measures relevant to patient-centered care and outcomes of early palliative care, cost of personnel, staffing, and limited space for service delivery. Potential facilitators to implementation include decision aids and shared decision-making process, planned communication and coordination between health care team, flexibility in core clinical components, and elements of palliative care rated highly by patients that may help "sell" providers. Performance measures relevant to patient-centered care and outcomes of early palliative care may also be a potential facilitator to implementation; however, in the VHA there are currently no standardized performance measures.

Quality of Evidence for KQ 3

The ROB was judged low for all studies.[49-52] Detailed ROB descriptions are given in Tables 6 and 7.

Table 6. ROB for KQ 3 Studies with Qualitative Designs[32]

Study	Clear Statement of Aims	Appropriate Qualitative Method	Appropriate Research Design	Appropriate Recruitment Strategy	Data Collected Addressed Research Issue	Sufficiently Rigorous Data Analysis	Overall Risk of Bias
Maloney, 2013[51]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Bakitas, 2016[50]	Yes	Yes	Yes	Yes	Yes	Yes	Low
Bekelman, 2016[50]	Yes	Yes	Yes	Yes	Yes	Yes	Low

Table 7. ROB for KQ 3 Study with Retrospective Cohort Design[31,32,54]

Study	Selection of exposed and nonexposed drawn from the same population	Confident in assessment of exposure	Confident that outcome of interest was not present at start of study	Exposed and nonexposed matched for all variables or controlled for prognostic variables	Confident in assessment of prognostic factors	Confident in assessment of outcome	Adequate follow up of cohorts	Cointerventions were similar between groups	Overall Risk of Bias
Sharma, 2016[52]	Definitely Yes	Definitely Yes	Definitely Yes	Mostly Yes	Definitely Yes	Definitely Yes	Definitely Yes	NA	Low

SUMMARY AND DISCUSSION

We evaluated palliative care integrated with oncology care for patients with symptomatic or advanced cancer, examining effects on a range of outcomes of importance to patients, clinicians, and policymakers. Our review is unique in its focus on integrated approaches for patients with advanced cancer, classification of the level of integration, and inclusion of studies that address barriers and facilitators to palliative care. We identified 7 RCTs and 2 cluster-randomized trials, all of which were comparative effectiveness trials and examined palliative care services that were moderately integrated with oncology care. We found a pattern of positive effects, including lower mortality and improved short-term QOL. Other outcomes were reported less frequently, and intervention effects could not be determined definitively.

We were particularly interested in describing intervention elements that were associated with greater benefit to patients with cancer. Most of the trials did not describe integration elements carefully. Therefore, we relied on author report to classify the level of health care integration. We qualitatively examined associations between integration elements, palliative care intervention domains, and intervention impact (based on cross-case impact analyses). There was no clear association between level of integration and intervention effects, but these analyses were limited by the small number of studies and lack of variability in integration elements. We identified and qualitatively examined 4 studies that describe barriers and facilitators to implementing integrated palliative and oncology care. Findings for each Key Question (KQ) are summarized in the sections below.

SUMMARY OF EVIDENCE BY KEY QUESTION

KQ 1—Effect on Patient and Caregiver Outcomes

In all trials, palliative care interventions were delivered by multidisciplinary teams; however, aspects of the palliative care interventions (eg, intensity and level of integration) varied across trials. All interventions were colocated in the same facility and were classified as moderately integrated with palliative care services. Integrated palliative care improved short-term QOL for patients with advanced cancer. Improvements in overall symptom burden were found in all but 1 study, a finding confirmed by a meta-analysis that excluded this outlier study. Integrated palliative care decreased all-cause mortality, and among those who died, increased the likelihood of dying at home. Palliative care that included a specific caregiver intervention improved short-term caregiver depressive symptoms. Caregiver experience was improved in the single trial reporting this outcome. Palliative care did not improve other patient or caregiver outcomes or utilization outcomes; however, given that these outcomes were reported in only a small subset of studies, analyses were likely underpowered to detect effects.

Strength of evidence (SOE) was rated for primary outcomes (QOL and symptom burden) and mortality on the basis of study design, ROB, consistency, directness, and precision (Table 8). The SOE was rated high for effects on mortality and moderate for short-term QOL. SOE was low for long-term QOL and very low for overall symptom burden. SOE was not rated for adverse effects because no studies reported this outcome. Concerns that contributed to the lower SOE were high ROB and imprecision that was attributed to the 95% CI not excluding a small and small-to-moderate effect.

Table 8. Strength of Evidence for Effects of Integrated Outpatient Palliative Care and Oncology in Symptomatic or Advanced Cancer

Outcome	Number of RCTs (Patients)	Findings[a]	Strength of Evidence (Rationale by Domain)
Quality of life, short-term (follow-up range 1 to 3 months)	9 (1487)	SMD 0.24 higher (0.13 higher to 0.35 higher)	Moderate SOE serious ROB, consistent, precise
Quality of life, long-term (follow-up range 27 weeks to 13 months)	5 (549)	SMD 0.15 higher (0.12 lower to 0.43 higher)	Low SOE serious ROB, consistent, imprecise
Overall symptom burden (follow-up range 1 to 3 months)	5 (837)	SMD 0.25 lower (0.39 lower to 0.11 lower)	Very low SOE serious ROB, inconsistent, imprecise
Mortality (follow-up range 12 to 36 months)	4 (866)	HR 0.77 (0.61 to 0.98) 96 fewer deaths per 1,000 patients (7 to 179 fewer deaths)	High SOE low ROB, consistent, precise

[a] SMD reported is from the sensitivity analyses excluding the single high risk of bias study.
Abbreviations: RCT=randomized controlled trial; ROB=risk of bias; SMD=standardized mean difference; SOE=strength of evidence

KQ 2—Assessment of Integration Elements on Outcomes and Impact

Published trials of palliative care do not routinely describe elements of integration with oncology care. Integration was classified based on unpublished information from authors. We used a previously developed integration framework that classifies studies into 6 levels along a continuum of basic communication among providers to fully shared systems and resources with equal roles across providers. Data for 6 of the 9 studies were available. In these 6 trials, palliative care and oncology teams were colocated in the same facility and exchanged information in a standard and routine manner. The majority of studies involved close onsite collaboration with some systems integration; no interventions were classified as fully integrated. Regarding aspects of palliative care included in the study interventions, all interventions included physical and psychological aspects of care; none included cultural aspects of care. No association between integration level and intervention outcomes were found; however, power to detect treatment effects was limited by the small number of studies and limited variability in integration levels.

KQ 3—Assessment of Barriers and Facilitators to Implementation

Only 4 studies addressed barriers or facilitators to integrated palliative care in VA, with only 1 study being designed specifically to address this objective. Three studies enrolled Veterans, and 1 study enrolled VA health care providers and health system leaders. Common barriers to implementation included lack of performance measures for patient-centered care and outcomes, cost of personnel, limited staffing and space, low participation by patients in shared medical appointments, and perceptions that palliative care is limited to end stages of disease. Results from 1 study found that older Veterans with advanced cancer are referred to palliative care earlier than younger Veterans. Thus, younger age among Veterans may be a barrier to either referral to and/or readiness to accept palliative care services. A patient decision aid that introduced palliative care was viewed favorably by patients and may facilitate engagement in

services. Facilitators to implementation identified by VA leaders included communication and collaboration between health care leaders, and patient-provider education about roles and responsibilities of palliative and oncology teams.

CLINICAL AND POLICY IMPLICATIONS

The VA does not have current guidelines that address provisions for standard integration of outpatient palliative care into routine oncology care. Guidelines from professional societies, including American Society of Clinical Oncology (ASCO),[8] National Comprehensive Cancer Network (NCCN),[55] Oncology Nursing Society (ONS),[9] and American College of Surgeons Commission on Cancer[10] all recommend routine integration of palliative care with oncology services. Our results, and the findings of recent systematic reviews and meta-analyses,[15,56,57] support these recommendations in demonstrating QOL improvements with integrated care. Although we did not observe benefits for symptom burden, we are among the first to find an aggregate improvement in survival across multiple trials in the oncology setting. This effect on survival differs from a recent Cochrane review that focused narrowly on early palliative care for patients with advanced cancer. This discrepancy is related to differences in the studies evaluated: one study[58] included in the Cochrane analysis did not meet our eligibility criteria, and some studies included in our analyses were either not published at the time of the Cochrane review[45] or were excluded from their review.[39] Negative outcomes (*eg,* 6-12 month QOL, caregiver well-being) outside of the short-term setting should be interpreted with caution, given the shorter-term focus of most trials in this area. Our findings suggest an important role for consistent integration of palliative care into routine outpatient oncology care, which should be considered in applicable policies and clinical practices in VA. Similar to the recent Cochrane Review,[56] we were not able to isolate care components or integration elements associated with greater intervention effect.

LIMITATIONS

Our protocol-driven review has a number of strengths, including input from an expert panel, new data gathered from study authors, rigorous methods, examination of barriers and facilitators to implementation, and a novel approach to evaluating the key elements of integrated palliative care. This novel approach allowed for a theory-driven, standardized classification of each study intervention. A significant limitation of this approach is that we relied on authors' retrospective reports about aspects of integration that were used to classify each study. Additionally, a broad definition of colocation (*ie,* in the same facility) was used and limited variability in author responses to this item. Thus, it is possible that degree of the physical proximity was diverse and could account for some variability in the impact ratings. Further, all of the included studies described interventions as being colocated, and a non-colocated intervention was not available for comparison. We limited our review to English-language publications, which may have excluded potentially informative evidence. Other limitations are described below.

Publication Bias

Given the small number of studies, statistical methods to detect publication bias are not useful. Other strategies, such as searching ClinicalTrials.gov for completed but unpublished studies is not a particularly effective way to identify publication bias. Thus, although no publication bias was detected, tools for detection are poor.

Study Quality

We were also limited by the existing literature. We identified few studies, and several were assessed as unclear ROB. High attrition and incomplete data, inadequate or unclear allocation concealment, and outcome assessments that were not clearly blinded to intervention assessment within trials contributed to judgments of higher risk. Palliative care intervention components and integration elements were poorly defined in most studies; 3 of the 9 study authors did not respond with information about integration elements. Some outcomes of interest, such as caregiver outcomes, were infrequently reported. No studies reported adverse effects.

Heterogeneity

We compared interventions that varied substantially in goals, delivery, intensity, and target recipient. We found that interventions varied in intensity, frequency of contact, duration, delivery mode, goals, and outcome measures used. Despite variability in intervention design characteristics, effects on most outcomes were consistent. We also compared outcome measures that may not have precisely measured the same constructs, though we attempted to pool only measures that were conceptually similar. Additionally, although no intervention effect was found on long-term quality of life, research has not examined the appropriateness of this outcome for patients in the late stages of terminal illness. Thus, it is unclear whether long-term quality of life would be expected to increase as patients approach death.

Applicability of Findings to VA Population

Two (22%) of the 9 studies examining the effects of integrated palliative and oncology care and 3 (75%) of the 4 studies describing barriers and facilitators to implementation of integrated care included Veteran samples. Eleven studies were conducted in North America, and the other 2 studies were conducted in economically developed countries. Identified studies included predominantly white samples, and it is unclear whether the findings generalize to individuals from other ethnic and racial groups.

RESEARCH GAPS/FUTURE RESEARCH

We structure our reflection of gaps in evidence by considering each element of the PICOT framework (Table 9). Although it would be possible to generate an extensive list of gaps in evidence, we restricted this list to the areas judged to be highest priority, given the current state of evidence. To facilitate future literature syntheses, we encourage investigators conducting clinical trials to include these studies in trial registries.

Table 9. Highest Priority Evidence Gaps

PICOT Domain	Evidence Gap
Population	Research needed with ethnically, racially, socioeconomically diverse groups of people. Evaluate potential differential intervention effects by type of malignancy.
Interventions	More clearly defined integration elements and aspects of intervention are needed. More clearly defined methods could reduce uncertainty about the relationship between outcomes and intervention dose, mode of delivery, and components. Study designs are needed to incorporate patient and caregiver/stakeholder input on barriers and facilitators to implementation.

PICOT Domain	Evidence Gap
Comparators	Inpatient palliative care may also be considered as a comparator; non-colocated integrated care interventions could also be compared to colocated integrated care interventions.
Outcomes	Few studies report caregiver outcomes. Outcome measures vary greatly across studies making synthesis difficult. Research is needed on outcomes most valued by patients with advanced cancer, and how to best measure these outcomes, including the respondent (patient or caregiver) and measures that account for the unique characteristics of this population.
Timing	Short-term outcomes may be most useful for this patient population.
Setting	Research on integration between palliative and oncology care in community settings is needed. VA and other funding agencies may consider a comparative effectiveness trial.

The VHA may be uniquely well-suited to addressing these gaps in evidence. A key component of the Quality Enhancement Research Initiative (QUERI) program[59] is to advance implementation science and identify effective strategies for implementing effective interventions. Our review supports integrated palliative care as an effective intervention, and thus it is well-suited to a test of implementation strategies. However, palliative care does not appear to be a particularly good fit into any of the 15 existing QUERI Centers, so to pursue this, it is likely a new QUERI Center would need to be formed to focus on this issue. QUERI has also developed innovative partnerships between health services investigators and program offices in VA to evaluate the effectiveness of new programs and initiatives. Partnerships in this area would have the potential to test the effects of real-world implementation of integrated palliative care and to conduct evaluations to better identify the key components of palliative care and integration that are associated with the most effective programs.

CONCLUSIONS

There is a small but growing literature about integrated palliative and oncology care interventions for patients with symptomatic or advanced cancer. Overall, we identified a diverse set of interventions that showed moderate levels of integration. These interventions demonstrated a pattern of small-to-moderate, positive short-term effects on mortality and on outcomes that are important to patients. Effects on other outcomes, such as health care utilization and caregiver outcomes, are less well studied. However, considerable gaps remain in the evidence for critical intervention elements and some policy-relevant outcomes. More clearly defined palliative care intervention characteristics and integration elements would allow for a more precise understanding of the impact of integrated palliative and oncology care on outcomes. New studies should report both intervention elements and integration elements more carefully, adopt a standard set of outcomes, and attend to recruiting from a more racially and ethnically diverse population.

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