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1. Review evidence concerning health outcomes associated with the early integration of palliative care with standard oncology care for patients with advanced cancer.
2. Discuss barriers to the early integration of palliative care with standard oncology care for patients with advanced cancer.

ARTICLE TITLE: Early Integration of Palliative Care Services With Standard Oncology Care for Patients With Advanced Cancer

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Early Integration of Palliative Care Services With Standard Oncology Care for Patients With Advanced Cancer

Joseph A. Greer, PhD1; Vicki A. Jackson, MD, MPH2; Diane E. Meier, MD, FACP3; Jennifer S. Temel, MD4

Scientific advances in novel cancer therapeutics have led to remarkable changes in oncology practice and longer lives for patients diagnosed with incurable malignancies. However, the myriad options for treatment have established a culture of cancer care that has not been matched with a similar availability of efficacious supportive care interventions aimed at relieving debilitating symptoms due to progressive disease and treatment side effects. Accumulating data show that the introduction of palliative care services at the time of diagnosis of advanced cancer leads to meaningful improvement in the experiences of patients and family caregivers by emphasizing symptom management, quality of life, and treatment planning. In this review article, the rationale and evidence base for this model of early palliative care services integrated into standard oncology care are presented. In addition, the implications and limitations of the existing data to 1) elucidate the mechanisms by which early palliative care benefits patients and families; 2) guide the dissemination and application of this model in outpatient settings; and 3) inform health care policy regarding the delivery of high-quality, cost-effective, and comprehensive cancer care are discussed.

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Introduction

Significant innovation in the development of combined and targeted chemotherapy regimens over the last 2 decades has resulted in a broader array of efficacious treatments and longer life in patients with advanced cancer.1 While advances in cancer therapy hold promise for arresting disease progression, the state of science and research development has lagged in targeting the physical, psychosocial, and existential elements of living with advanced cancer.2 Even with growing recognition and recommendations for addressing the supportive care needs of patients with advanced cancer, the disparity in comprehensive cancer care persists for this vulnerable population due to several factors. Among them are the lack of trained professionals to undertake research and clinical care, a paucity of evidence to guide the delivery and dissemination of supportive care services, and limited funding for developing and testing interventions to alleviate symptoms and enhance quality of life.4–6 To overcome this critical gap in cancer care, one approach that has received considerable attention in recent years is the early integration of palliative care services with standard oncology care soon after the diagnosis of advanced cancer.7

Typically, a multidisciplinary team of physicians, nurses, social workers, and chaplains deliver palliative care services, which focus on symptom management, psychosocial support, and assistance with treatment decision-making for patients with serious illnesses, their families, and their other health care providers.8 As affirmed by the World Health Organization, palliative care is appropriate for delivery early in the course of disease and alongside life-prolonging treatments.9 Palliative care emphasizes the well-being of patients and families coping with a serious medical illness at any point along their disease trajectory, whether the goal is cure, living with cancer as a chronic disease, or responding to...
progression of illness. Although palliative care is a new medical specialty as of 2007, the number of specialists and programs has increased considerably in the last decade. Most large (more than 300 beds) hospitals and National Cancer Institute-designated cancer centers (85% and 98%, respectively) report having palliative care programs, which are predominantly comprised of inpatient consultative teams.11,12,14

In recent years, researchers have begun testing the feasibility and efficacy of innovative models of palliative care delivered simultaneously with oncology care in the ambulatory care setting. The Center to Advance Palliative Care has described 3 models for delivering outpatient palliative care within hospital or health system structures: stand-alone, colocated, or fully embedded clinics. Whereas stand-alone clinics are administered separately from other specialty services, colocated clinics may share office space, overhead costs, and clinical operations staff with the host specialty. Fully embedded (integrated) clinics are also colocated in specialty practices but have the added advantage of coordinating treatment protocols, implementing common clinical pathways, and improving communication between specialists.15

Clinicians trained in palliative care are uniquely positioned to comanage with other specialists many of the supportive care needs of patients with advanced cancer and their families. Comanagement describes the close clinical collaboration between the palliative care specialist and the primary or referring clinician in delivering patient care. While each member provides input in managing different aspects of treatment, overall responsibility lies with the primary/referring clinician.15 The goal of comanagement between oncology and palliative care is to support and enhance quality of life by relieving symptoms associated with cancer and its treatment effects.10,16 Such services not only benefit patients with poor-prognosis metastatic cancer but also should be considered for those who have localized disease, those who may be cured (eg, patients with acute leukemia or lymphoma), or those who will live for years with cancer as a chronic disease.17 Palliative care clinicians are well suited to fill this critical role in comprehensive cancer care given their specialized training in managing medical symptoms, delivering psychosocial and spiritual support, assisting with complex treatment decisions, and working collaboratively as part of a team and with other clinical specialists. Finally, palliative care clinicians consider the family as the unit of care, providing counseling, education, and support also to caregivers, who are at high risk of social, financial, practical, and illness burden and distress.8,18

Persistent misconceptions regarding the role of palliative care providers and the goals of such treatment complicate the integration of these services into other medical practices. Many oncologists tend to refer patients to specialized palliative care services only for uncontrolled symptoms or late in the course of disease when planning discharge. Yet emerging evidence has shown that the introduction of palliative care services early in the course of advanced cancer improves a number of salient outcomes, such as quality of life, symptom burden, mood, and use of health care services. As a result, an expert panel of the American Society of Clinical Oncology recently recommended that patients with metastatic non-small cell lung cancer (NSCLC) should be offered concurrent palliative and oncologic care from the time of diagnosis and that such combined treatment should be considered for any patients with metastatic cancer early in the course of disease. In this article, we present the rationale and extant data supporting the early palliative care model. In addition, we discuss the implications and limitations of the findings to 1) elucidate the mechanisms by which early palliative care benefits patients and families; 2) guide the dissemination and application of this model in outpatient settings; and 3) inform health care policy regarding the delivery of high-quality, cost-effective, and comprehensive cancer care.

Rationale for the Early Integration of Palliative and Oncology Care

Symptom Burden in Patients With Advanced Cancer

When patients initially present with advanced cancer in the medical setting, the focus of the oncology care team is rightly placed on establishing an accurate histologic diagnosis, staging the disease, and developing a plan for potential cancer therapies. At such times, patients are often experiencing profound emotional and spiritual distress as well as physical symptoms that may limit functioning and impair their quality of life. Common symptoms in patients with advanced cancer include fatigue, pain, weakness, loss of appetite, and lack of energy, although these vary by demographic and disease characteristics such as age, gender, cancer site, and performance status. Moreover, symptoms increase in frequency as patients approach the end of life.28

For many patients and family caregivers, the physical burden of advanced cancer is compounded by psychological distress. Approximately 30% of patients in palliative care settings experience some combination of depression, anxiety, and/or adjustment disorder. Such psychological morbidity can be associated with challenges in the physician-patient relationship. For example, patients with advanced cancer who have anxiety disorders report less trust in their physicians, in addition to expressing concern that their symptoms would not be adequately controlled. The presence of psychiatric disorders in patients with advanced cancer is also associated with a higher likelihood of psychiatric disorders in their informal caregivers. The stress of taking care of a loved one...
with a serious illness like cancer is associated not only with depression, anxiety, and other mental health problems but also with an increased risk of morbidity and medical illness among family caregivers.18,32

Some data suggest that oncologists fail to screen adequately for psychosocial distress in their patients with cancer.33 Similarly, while oncologists’ perceptions of their ability to relieve cancer-related pain have improved in the last 2 decades, persistent barriers hamper adequate management, such as poor assessment and a reluctance to prescribe opioids.34,35 A national survey of oncologists shows that only a minority report that they frequently refer patients with cancer to pain or palliative care specialists.35 Limited access to palliative care experts in community hospitals is certainly one barrier to referral.12 However, even in resource-rich comprehensive cancer centers, referrals to palliative care tend to occur late in the course of disease, if at all.36 In addition, low referral rates are associated with oncologists’ beliefs that a palliative care consultation might alarm patients and families, whom they believe wish to focus exclusively on curative treatment and not prognosis.37 The medical literature does not support the same sample revealed that initial visits with palliative care clinicians focused on building relationships and rapport by listening to patients and families describe what is important to them, establishing illness understanding and education (median, 10 minutes).38 A longitudinal qualitative analysis of the relative time spent discussing different topics during initial consultations was as follows: symptom management (median, 20 minutes), patient and family coping (median, 15 minutes), and illness understanding and education (median, 10 minutes).38 A longitudinal qualitative analysis of the same sample revealed that initial visits with palliative care clinicians focused on building relationships and rapport by listening to patients and families describe what is important to them, establishing illness understanding and preferences for receiving information, and discussing the impact of cancer treatments. While addressing symptom burden was prominent across all sessions with palliative care, discussions about resuscitation preferences and end-of-life care planning typically occurred close to the end of life during the final visits to the cancer center.39

In the outpatient oncology setting, palliative care clinicians begin their therapeutic relationships with patients and families by emphasizing their explicit aim of helping individuals with newly diagnosed metastatic cancers to live as well as they can for as long as they can, especially while undergoing challenging cancer therapies. In this era of advancing science and a rapidly aging population with a high incidence of cancer, a single oncology clinician may not be able to manage all aspects of cancer care, ranging from diagnosis and chemotherapy administration to symptom management and discussions about care at the end of life. Additional clinical support from palliative care throughout the entire disease trajectory may serve as one approach for not only identifying and alleviating the burden of debilitating symptoms but also helping oncology teams achieve the highest quality standards for comprehensive cancer care.

Prognostic Awareness and Treatment Decision-Making

Alongside the oncology team, palliative care clinicians play a pivotal role in clarifying patients’ understanding of their prognosis, thereby empowering those with serious and incurable diseases to make informed treatment decisions. Studies show that patients with advanced cancer and their families report a desire to receive timely and realistic prognostic information.40–45 Greater than 95% of individuals with cancer want their physician to be realistic and believe that they should be told if their illness is terminal, with the majority endorsing that the information should be communicated immediately after diagnosis.42,46 However, patients with metastatic cancer and their families often fail to comprehend the goals of therapy, maintaining inaccurate illness perceptions and expectations about the purpose of treatment.47,48 For example, in a recent large, national, prospective cohort study, the majority of patients with metastatic lung (69%) and colorectal (81%) cancers failed to understand that chemotherapy was not at all likely to cure their cancer.49

Importantly, patients’ understanding of their illness and prognosis is reported to strongly predict treatment decision-making.50–52 While patients with advanced cancer who view themselves as terminally ill are more likely to prefer and receive symptom-directed care at the end of life, those who overestimate their prognosis are more likely to receive cancer-focused therapy of unclear benefit during the last month of life.53,54 Similarly, patients with metastatic cancer who overestimate their chances of survival are significantly less likely to discuss hospice and advance care planning with physicians compared with patients who have more realistic views of their prognoses.48 The comorbidity of clinically significant mood symptoms may also impact decision-making, as patients with depression or anxiety are more likely to receive chemotherapy near the end of life than patients without psychological distress.55

Although the majority of oncologists state that they typically provide accurate prognostic information to patients with terminal cancer, data point to the contrary and suggest that clinicians routinely communicate overly optimistic survival estimates to patients.56,57 In addition, many physicians report that they provide prognostic information only upon a patient’s explicit request or when no further treatment options are available.48 However, such
communication patterns may be problematic, since patients prefer that physicians initiate discussions about prognosis and what they can realistically expect early in the course of treatment. The disconnect in communication between patients and clinicians also impedes treatment decision-making. Avoidance of conversations regarding prognosis and care preferences between oncologists and patients also limits discussion and documentation of patients’ goals for care vis-à-vis quality and quantity of life tradeoffs as articulated in advance directives. Communicating about these wishes is essential given that only 20% of ambulatory patients diagnosed with various metastatic cancers at an academic medical center had a resuscitation preference documented in their electronic medical record.

A repeatedly cited barrier to effective communication about preferences for care, including advance directives, is the concern among oncologists that such conversations may cause patients to feel distress or lose hope; however, depression and worry are not reported to be higher in patients who report having end-of-life discussions with their physicians. In fact, those patients with advanced cancer who express acceptance of their prognosis are less likely to feel depressed, anxious, or hopeless. Importantly, studies show that patients who recalled discussing plans for end-of-life care received less aggressive care near death and were more likely to have an earlier referral to hospice and to experience a better quality of death.

With the early involvement of palliative care, patients with advanced cancer and their families have the opportunity to develop a long-standing relationship with members of the palliative care team. Developing this therapeutic alliance helps to build trust that facilitates difficult conversations regarding prognosis as well as the process of weighing the risks and benefits of different treatment options in the context of the patient’s and family’s goals for care. Moreover, palliative care clinicians are able to support the oncology team’s effort to communicate accurate information about prognosis, especially since achieving such an understanding often requires multiple conversations and an evolution in awareness and emotional acceptance. That is, the delivery of prognostic information is more of a process than a single event, with consideration of patients’ preferences for the amount and timing of information they desire. In addition, in a comanagement model with oncology, palliative care teams have the role and credibility to assist patients and their families manage symptoms, discuss goals of care, and make informed treatment decisions. Nonetheless, this role is distinct from that of oncologists, who patients expect to focus on directing cancer therapy, stabilizing disease, and prolonging life. At times, patients and their families may filter their concerns regarding symptoms, disease burden, and an uncertain future for fear that the oncology team may abandon or “give up” on them. The parallel clinical relationship with palliative care, whose primary focus is on enhancing quality of life through improved symptom management and psychosocial support, provides a natural opportunity for patients and their families to clarify questions about prognosis and discuss openly their concerns, symptom burden, fears, and treatment wishes.

Resource Use, End-of-Life Care, and Treatment Costs

The involvement of palliative care clinicians in conversations about prognosis not only informs understanding of patient illness and treatment decision-making, but also potentially mitigates the concerning trend of continuous and costly cancer treatment beyond the point of evidence of benefit. Oncology care for patients with advanced cancer is becoming increasingly intensive, with greater use of multiple cancer regimens and the administration of chemotherapy only weeks from the end of life. Over the decade of the 1990s, rates of admission to the hospital, emergency department, and intensive care unit for patients with cancer during the final month of life increased as well. Unfortunately, near-death cancer treatment is not only associated with worse quality of life in patients with advanced cancer and lower caregiver satisfaction with end-of-life care, but also fails to improve survival. Such intensive treatment often results in late hospitalizations and intensive care unit admissions, placing family caregivers at an increased risk of psychiatric illness, such as major depression and complicated bereavement.

The administration of chemotherapy and inpatient stays near the end of life also prevent, delay, or interrupt referrals to hospice services. Hospice agencies in the United States are paid a standardized per diem rate of approximately $160 per day, and therefore generally lack the financial resources to provide cancer therapy. Late referral to hospice services prevents patients from accessing comprehensive supportive care that benefits the entire family. Specifically, family members of patients who receive hospice services not only report greater satisfaction with care and a higher quality of death for the patient, but also experience improved psychological and physical health outcomes compared with those caring for patients who do not receive hospice. Data also suggest a survival advantage among patients with certain advanced cancers who are referred to hospice compared with similar controls receiving usual care. Thus, the American Society of Clinical Oncology Quality Oncology Practice Initiative has recognized several key metrics for determining high-quality end-of-life care, including no chemotherapy in the last 14 days of life, enrollment in hospice services, and a length of stay in hospice of greater than 7 days. To achieve these quality metrics, palliative care clinicians working in concert with the oncology team may assist patients and families in the shared decision-making process regarding the
optimal timing for transitioning from disease-modifying therapy to hospice care.

Maximizing the delivery of high-quality care at the end of life is also a top priority for slowing the unsustainable growth of health care costs. Over the last decade, the frequency of high-cost imaging in patients with metastatic cancers has increased, and researchers have estimated the mean total health care expenditures for patients with metastatic lung and breast cancers to be greater than $125,000 and $128,000, respectively. In addition, patients who report inadequate support for their religious and spiritual needs from clinic staff have higher costs for medical care in their last week of life compared with those who receive such support. The Palliative Care Leadership Centers’ Outcomes Group recently demonstrated that palliative care consultations for hospitalized patients result in significant cost savings. Study findings revealed that health care expenditures began to decline 24 to 48 hours after the palliative care consultation, confirming that the reduced health care costs were most likely due to recommendations of the palliative care team. Some data also suggest lower costs and resource use with community-based palliative care. Moreover, researchers have shown that patients with advanced cancer who recalled having a conversation regarding their end-of-life care preferences received less aggressive medical care in the last week of life compared with patients who did not recall these conversations, with a substantial cost savings. Unfortunately, many discussions about end-of-life care for patients with advanced cancer occur in the acute hospital setting and late in the course of illness.

Evidence Base for the Early Integration of Palliative Care Services

To help improve symptom management, reduce psychological distress, and enhance treatment decision-making for patients with advanced cancer, researchers have begun to propose and test new models of comanagement between oncology and palliative care. Several comprehensive literature reviews have been published in the last 5 years regarding the efficacy of palliative care to improve outcomes in patients with serious illnesses. However, few of these investigations tested the effects of specialized palliative care interventions in patients with cancer, and most studies were replete with methodological weaknesses. Moreover, only one study to date has focused on the early integration of specialized palliative and oncology care soon after diagnosis for patients with metastatic cancer.

Before discussing the specific evidence regarding the early integrated model, we will summarize findings from the recently published reviews of palliative care in general. First, Zimmermann et al conducted a systematic review of the effectiveness of specialized palliative care, identifying 22 randomized controlled trials that met inclusion criteria. Although the authors found reliable evidence for the effectiveness of specialized palliative care in improving family satisfaction with care, the results were less conclusive with respect to quality of life (only 4 of 13 studies showed a significant benefit) or symptoms (only 1 of 14 showed a significant benefit) in patients with diverse illnesses, including cancer. However, small sample sizes and inadequate statistical power to detect differences limited the conclusions of many studies. More recently, Higginson and Evans conducted a systematic review to examine whether specialist-delivered palliative care improves outcomes (such as pain, symptoms, quality of life, and resource use) for patients with cancer and their families in a range of care settings. Of the 8 randomized controlled trials that met inclusion criteria, only 3 showed significant benefit for the quality-of-life and symptom control outcomes. Finally, El-Jawahri et al reviewed the evidence from 22 randomized controlled trials testing the effects of palliative care on a number of outcomes (quality of life, physical and psychological symptoms, and satisfaction with care, among others) in patients with incurable illnesses. The authors included studies of palliative intent as well as those of specialized palliative care, observing more consistent evidence for the benefit of interventions to improve quality of life (5 of 7 studies showing a significant improvement) and satisfaction with care but not physical or psychological symptoms.

Evaluating the research pertaining to specialized palliative care is challenging given the diversity and lack of standardization of interventions and outcome measures reported in the literature. In addition, the interpretation of results is limited by numerous methodological weaknesses of clinical trials, including biased recruitment methods, poor specification of protocols, problems with adherence, contamination between study groups, inadequate statistical power, and marked attrition. Finally, existing evidence supporting early and concurrent palliative and oncology care predominantly comes from a few pilot feasibility studies and 2 randomized controlled trials, one of which represented a psychoeducational palliative intervention and one of a specialized palliative care team comanaging comprehensive treatment with oncologists in an ambulatory cancer center.

Demonstration of the Feasibility of Early Outpatient Palliative Care

Both retrospective and prospective cohort studies show that outpatient palliative care consultations at comprehensive cancer centers are associated with improvement in a number of physical and psychological symptoms, such as pain, fatigue, depression, and anxiety. While these investigations suggest the benefit of referring patients with advanced cancer to specialized palliative care clinics that are stand-alone or
colocated in the ambulatory care setting, other pilot studies point to the feasibility and promise of embedded or integrated palliative care services in private office-based oncology practices and community cancer centers.100–103 In contrast, Meyers et al conducted a nonrandomized pilot trial to examine the feasibility and preliminary results of a home-based, simultaneous care model in 44 patients with advanced cancer receiving investigational cancer therapy compared with a usual-care cohort.104 The simultaneous-care intervention included multiple weekly home visits with a nurse trained in both cancer chemotherapy and palliative care as well as with a clinical social worker for patients undergoing investigational cancer therapy protocols. Although hospice enrollment was higher in the simultaneous-care group compared with the usual-care group, quality of life did not differ between conditions.104 Given the paucity of data to date as well as the variability in the setting (eg, stand-alone vs integrated vs home-based), timing (upon referral vs simultaneous), and type of intervention (nurse- and social worker-directed vs specialty trained palliative care clinicians), meaningful interpretation of these findings is limited with respect to supporting the early palliative care model.

Finally, as an initial feasibility test of early palliative care, Temel et al conducted a phase 2 study to investigate the integration of specialized palliative care services for patients who were newly diagnosed with advanced NSCLC.65 Specifically, 51 patients with good performance status enrolled in the study within 8 weeks of diagnosis, receiving integrated palliative and oncology care throughout the course of their disease at an academic cancer center. Over a 6-month period, participants attended monthly consultations with clinicians from the specialized palliative care team and completed self-report assessments of quality of life and mood. Demonstrating the feasibility of early integrated and simultaneous care, the investigators reported that more than 85% of the study patients were able to complete the majority of palliative care visits as well as the assessments of quality of life and mood symptoms. Even at baseline, a notable percentage of patients were experiencing symptom burden and psychological distress.65

**Efficacy of Early Integrated Palliative Care**

Two randomized controlled trials have been published in which investigators examined palliative care interventions delivered early in the course of disease and simultaneously with oncology care.7,20 The first, led by Bakitas et al,20 tested the effects of a psychoeducational intervention consisting of telephone-administered educational sessions with nurse practitioners for a large sample of patients with mixed types of advanced cancer. Temel et al7 conducted the other clinical trial, which examined the efficacy of integrating specialized palliative and oncology care in the outpatient setting for individuals newly diagnosed with metastatic NSCLC.

In the Project ENABLE (Educate, Nurture, Advise, Before Life Ends) study by Bakitas and et al,20 investigators randomly assigned 322 individuals who were newly diagnosed with advanced gastrointestinal, lung, genitourinary, and breast cancers to receive a multicomponent nursing-led intervention in tandem with usual care versus usual care alone. For those in the intervention group, advanced practice nurses with palliative care training conducted 4 formal educational sessions with patients followed by monthly telephone contacts for ongoing case management, including assessing the need for further referral or resources, until the patients had died. Outcomes included quality of life, symptom intensity, mood, and resource use. The results of the trial showed that patients assigned to the intervention reported significantly better quality of life ($P = .02$), as measured by the Functional Assessment of Chronic Illness Therapy-Palliative Care, and mood ($P = .02$), using the Center for Epidemiological Studies Depression Scale, as well as a marginally significant effect for symptom intensity ($P = .06$) as per the Edmonton Symptom Assessment Scale. However, resource use (ie, days in the hospital and intensive care unit and number of emergency department visits) did not differ between groups. In addition, while a post hoc survival analysis showed that the median survival of patients who received the intervention was 14 months compared with 8.5 months for the usual-care group, this difference was not statistically significant ($P = .14$).

Investigating the early introduction of specialized palliative care, Temel et al7 randomly assigned 151 patients with newly diagnosed metastatic NSCLC to receive either early palliative care integrated with standard oncology care or standard oncology care alone at an outpatient academic cancer center. The study protocol required that patients assigned to the intervention meet with a specialty-trained palliative care physician or advanced practice nurse monthly throughout the course of disease until death. Although the visits with the palliative care clinicians were not scripted so as to allow tailoring of consultations to the individual needs of patients and families, the investigators adapted general guidelines for the clinical encounters based on the National Consensus Project for Quality Palliative Care.8 Initial consultations lasted a median of 55 minutes (range, 20 minutes-120 minutes), which primarily focused on building relationships and rapport, listening to the concerns of the patients and their families, managing symptoms, promoting illness understanding, and discussing the impact of cancer treatment.8,39 Across subsequent visits, the clinicians addressed various topics, including ongoing symptom management, coping with illness, cultivating understanding of disease status, and engaging family members.
End-of-life care planning, including decisions about resuscitation preferences and hospice, predominantly occurred in the late stages of illness during the final visits to the cancer center. The primary outcome of the study was change in quality of life, as measured by the Trial Outcome Index of the Functional Assessment of Cancer Therapy–Lung, from baseline to the 12-week assessment. Secondary outcomes included mood symptoms as well as various aspects of health care use. Investigators defined aggressive treatment at the end of life as participants receiving chemotherapy within 14 days of death and/or having no or very limited hospice services (ie, three days or fewer) prior to death.

The results of the study by Temel et al7 showed that participants assigned to the intervention reported a better quality of life over time, with higher scores at 12 weeks on the Trial Outcome Index ($P = .005$) when adjusting for baseline values in a linear regression analysis. In addition, rates of depression were significantly lower in the early palliative-care group compared with the standard oncology-care group, whether measured by the Hospital Anxiety and Depression Scale ($P = .01$) or the diagnostic threshold for the Patient Health Questionnaire–9 ($P = .04$). Within the subsample of participants who died by the time of analysis (N = 105), those assigned to early palliative care were less likely to receive aggressive treatment at the end of life ($P = .05$) and were more likely to have their resuscitation preferences documented in the outpatient electronic medical record ($P = .05$). Rates of anxiety as well as measures of health care use, including hospitalizations and emergency department visits, did not differ significantly between the study groups. Finally, a post hoc survival analysis showed that patients who received early, integrated palliative care had a longer median survival than those in the standard-care group (11.6 months vs 8.9 months; $P = .02$).

### Implication of Findings, Intervention Mechanisms, and Future Directions

#### Evaluation of the Evidence

The randomized controlled trials by Bakitas et al20 and Temel et al7 represent the most scientifically rigorous tests published to date of palliative care interventions delivered in tandem with standard oncology care early in the course of disease for patients with advanced cancer. The approaches of these investigations were quite different in that Project ENABLE20 used a nursing-led psychoeducational intervention over the telephone to empower and help patients advocate for themselves, whereas the trial by Temel et al7 evaluated the effects of a comanagement model of specialized palliative care integrated with standard oncology care in the outpatient clinic setting. Nonetheless, both studies demonstrate that such interventions can lead to meaningful improvements in quality of life, symptom burden, and mood for patients with advanced cancer who are undergoing active cancer therapies. Furthermore, although follow-up replication and confirmation are necessary, the study by Temel et al7 suggests that early integrated palliative care results in higher-quality end-of-life care and prolonged survival in patients with metastatic NSCLC.

Conducting palliative care research is fraught with multiple challenges related to the lack of standard definitions in the literature, problems with recruitment and attrition potentially creating selection bias, and methodological concerns with small sample sizes and inadequate statistical power, among others.105–108 Although the clinical trials by Bakitas et al20 and Temel et al7 have weaknesses that warrant cautious interpretation of certain findings, both studies possess a number of strengths that advance the study of palliative care. For example, the investigators of each study articulated well-defined primary and secondary outcome measures, as well as structured intervention protocols outlining the frequency of contact between participants and the palliative care clinicians. A noteworthy attribute of the study by Bakitas et al20 was the standardization of the intervention using didactic training, treatment manuals, and biweekly review of audiotaped educational sessions. In contrast, to ensure protocol adherence, the palliative care clinicians in the study by Temel et al7 recorded the time spent on addressing different topics with participants after each study visit, but further work is needed to elucidate the exact components of the integrated intervention.38 Both clinical trials included sufficient sample size calculations and power analyses for their primary outcomes. To overcome concerns related to attrition, Temel et al extended enrollment to achieve the desired sample size,7 whereas Bakitas et al had a somewhat smaller-than-planned sample size due to slow recruitment.20 Of note, both studies did limit the potential for selection bias by including intention-to-treat analyses for all participants and using recruitment methods that were not reliant on self- or provider referral. While the investigators in each trial clearly specified eligibility criteria for patients with advanced cancer, the final recruited samples were predominantly white, thereby limiting the generalizability of findings to patients of other races and ethnicities. Finally, although contamination between study groups has been a persistent concern in prior palliative care investigations, the study by Bakitas et al20 had no crossover between the study groups, and only a small percentage (14%) of the standard-care group in the study by Temel et al7 had one or 2 palliative care consultations by the 12-week assessment as per the clinical judgment of the treating oncologist.

### Potential Mechanisms by Which the Early Integration of Palliative Care Affects Outcomes

The mechanisms by which early palliative care interventions lead to improved outcomes in patients with advanced cancer remain unclear. Figure 1 depicts hypothesized...
relationships among intervention components and salient clinical outcomes. The improvements in quality of life and mood observed in the studies by Bakitas et al and Temel et al could be due to enhanced symptom management, greater human attention and social support, the provision of counseling, and improved coordination of care, although studies of intervention processes are needed to confirm such hypotheses. The findings of the study by Temel et al suggest that the positive effects on quality of life and mood in patients who received early palliative care were not due to increased prescriptions of psychotropic medications or referrals to mental health clinicians, which did not vary between groups. Moreover, neither clinical trial included information on comorbidities, rates of referrals to subspecialists, or types of pharmacotherapy for the management of symptoms such as pain or fatigue. Gathering such data in follow-up studies would help to clarify the ways that palliative care may improve quality of life by effectively identifying and relieving symptoms.

Consistent with recommendations from the American Society of Clinical Oncology Quality Oncology Practice Initiative, Temel et al also demonstrated better quality of care at the end of life with their intervention. In particular, compared with the standard-care group, patients who received early integrated palliative care had higher rates of resuscitation preferences documented in the ambulatory medical record as well as less cancer-directed treatment immediately prior to death. These outcomes may be due to 2 primary targets of the early palliative care intervention: improving illness understanding of patients and assisting with treatment decision-making. Some preliminary data lend credence to this possibility. In a subsequent analysis of the same sample of patients with metastatic NSCLC, Temel et al showed that approximately one-third of participants believed their cancer to be curable at the time of their baseline assessment, despite having already received a clear diagnosis of metastatic cancer and a treatment plan. Notably, across multiple follow-up assessments, a greater percentage of individuals assigned to the early palliative care group either maintained or developed an accurate perception of their cancer not being curable compared with those in the standard-care group (82.5% vs 59.6%; P = 0.02). This enhanced prognostic awareness may have facilitated discussions with the oncology team regarding the patients’ preferences for care at the end of life.

As a post hoc analysis, the survival advantage of patients with metastatic NSCLC who received early palliative care in the study by Temel et al requires replication. If confirmed, several mechanisms may account for the intriguing result. In a review of the literature, Irwin et al have outlined numerous potential pathways leading to prolonged survival in patients with metastatic NSCLC who receive early palliative care. Specifically, they examined the evidence for potential mediating mechanisms such as improving quality of life, controlling physical symptoms, reducing depression, and increasing social support, as well as impacting prognostic awareness and treatment decision-making at the end of life. Of note, in a secondary analysis of the study by Temel et al, Pirl et al found that the treatment of depression did not appear to account for the survival benefit from early palliative care. Examining biobehavioral models may also elucidate the complex relationships among cancer stress, behavior, and immune functioning in disease progression and survival. Another plausible explanation pertains to the administration of chemotherapy. Specifically, patients receiving the palliative care intervention may simply have had better management of symptoms and toxicities, allowing for more intensive cancer therapy throughout the course of disease. However, in a secondary analysis of the study by Temel et al, Greer

![Diagram of hypothesized relationships between early palliative care interventions and clinical outcomes.](image-url)
et al\textsuperscript{113} conducted a comprehensive review of patients’ electronic medical records, including all chemotherapy orders. This analysis revealed both groups to be similar with respect to the total number of regimens and time to the administration of second-line or third-line chemotherapy. Rather, the differences in chemotherapy administration between the study groups occurred at the very end of life. When evaluating the final chemotherapy regimen within 2 months of death, a significantly higher percentage of patients in the standard-care group received intravenous chemotherapy compared with those in the group receiving early palliative care (46.3% vs 24.2%; \(P = .01\)). Moreover, patients receiving early palliative care had a significantly longer enrollment in hospice services than the standard-care group, which also may have accounted for the survival benefit as some data suggest.\textsuperscript{82,83} Prospective research is nonetheless necessary to help oncology and palliative care clinicians discern with patients and families the optimal timing for ceasing cancer therapy and transitioning to hospice to maximize quality of life and perhaps even survival.

### Dissemination and Application of the Early Palliative Care Model in Oncology Settings

Despite the positive findings from recent research and calls for increased access to palliative care services in the community, most patients who are diagnosed with metastatic disease today will not have an opportunity to seek and obtain outpatient palliative care services. Certainly, the precise model for the efficient delivery of palliative care given the limited workforce and infrastructure has yet to be determined. As noted earlier, the Center to Advance Palliative Care has described 3 approaches (ie, stand-alone, colocated, and embedded clinics) for the delivery of outpatient palliative care in hospital or health system settings.\textsuperscript{15}

Similarly, Bruera et al\textsuperscript{114,115} have described 3 models for providing palliative services within oncology care: solo practice, congress, and integrated. While the solo practice model requires oncologists to manage all aspects of cancer care, the “congress” practice model stipulates that oncologists refer patients to multiple consultants for the management of pain, distress, fatigue, etc. Disadvantages of this approach include higher costs; more fragmented care; and an increased time commitment for patients and families, who must attend multiple appointments. Finally, integrated palliative care has the advantage of using the oncologist for cancer-specific treatments while the palliative care team attends to the patient’s physical symptoms and psychosocial concerns. With this model, the oncologist and palliative care physician can comanage care in a complementary manner, thereby reducing the need for the extensive use of outside consultants. Table 1 summarizes the potential advantages and disadvantages of different models for delivering simultaneous oncology and palliative care in the clinic and community settings.\textsuperscript{15,114,116}

The work of Temel et al\textsuperscript{7,65} undeniably bears out the benefits of the “integrated,” or “embedded,” model. With minimal intervention-related burden, patients in the study were able to meet with their assigned palliative care clinicians on the same day as, and sometimes in joint visits with, their oncologists. Such coordination has the potential not only to meet the supportive care needs of patients and families but also to ensure greater continuity and proactive planning of care, ideally staving off crises and unnecessary resource use.\textsuperscript{117}

Nonetheless, Kamal et al\textsuperscript{116} have identified potential downsides to integrated outpatient palliative care, such as the need for a higher patient performance status that is adequate for ambulatory care visits and a potential lack of continuity of care across clinical settings. Therefore, the authors propose a model for community- and home-based palliative care services. Such services would remain consistent across transitions to inpatient hospital and rehabilitation stays as well as home care, without regard to prognosis. Finally, the goal of community-based palliative care is to provide collaborative and coordinated care from a multidisciplinary team. Kamal et al\textsuperscript{116} cite the Project ENABLE model as an exemplar of rural community-based palliative care.

The timing of referral to palliative care will need further clarification as research provides evidence of optimal resource use. Although many physicians across specialties will possess certain essential skills and resources for delivering primary palliative care to the less-distressed patients, referral to secondary or tertiary care (in consultation or comanagement with palliative care specialists) or even admission to a palliative care unit may become necessary.\textsuperscript{118} Follow-up study is needed to discern the triggers and timing of such transitions for patients with advanced cancer, given the variation in life expectancies between individuals and across cancer types. One approach may be to consider decrements in functioning, persistent uncontrolled physical or psychological symptoms, or failure of first- or second-line chemotherapy as indicators for referral to palliative care.\textsuperscript{119} Given the limited availability of specialty-trained clinicians,\textsuperscript{4} it may not be feasible to provide extensive, frequent contact with the palliative care team throughout the course of illness for patients with advanced cancers who have an especially long estimated survival (eg, those with metastatic breast cancer). Therefore, enhanced skill and competency training in generalist-level palliative care is necessary for all clinicians who treat the seriously ill, including oncologists, mid-level providers, and cancer center staff. In addition, identifying clinically meaningful indicators or triggers for initiating outpatient specialty palliative care services may lead to the more efficient allocation of resources. Waiting until hospice referral would certainly be too late for patients and families to benefit from the provision of early palliative care.
Multiple challenges and unanswered questions remain regarding the development and dissemination of palliative care services for patients with advanced cancer. First and foremost, further research would help to elucidate the central components of the palliative care intervention that are most associated with improved outcomes. Such data would then ideally inform the allocation of resources and clarify the optimal models for the delivery of early palliative care, whether through nursing educational programs; consultative teams; and/or comprehensive, integrated palliative care programs. In addition, although the studies by Bakitas et al.\(^\text{20}\) and Temel et al.\(^\text{7}\) showed that patients with advanced lung, gastrointestinal, genitourinary, and breast cancers experienced positive outcomes from the provision of early palliative care, the degree to which patients with other cancer types or stages may benefit from the early introduction of such services has yet to be established.

### Delivery of High-Quality and Cost-Effective Comprehensive Cancer Care

Wide access to early, integrated palliative care for patients with advanced cancer and their families will be unlikely.
without health care delivery and payment reform, such as the inclusion of these services in bundled payments for an episode of cancer, as well as capitated, shared savings and global budget approaches resulting from the Patient Protection and Affordable Care Act. Traditional fee-for-service payments do not allow for the billing of insurance by some members of the palliative care team (eg, chaplains) or for interventions delivered via videoconference or telephone in some states. Thus, a model of payment that shifts the focus away from the volume of encounters and infusions by directing incentives toward quality of care will allow hospital systems to provide supportive care services that encompass the whole person as well as family caregivers.

Payment reform would ideally be accompanied by reforms in education and training, as more physicians, nurses, mental health clinicians, social workers, and chaplains need to establish basic competencies in delivering palliative care services. In addition to increasing coursework in medical and nursing school programs, intensive educational programs, such as the ACE Project (Advocating for Clinical Excellence: Transdisciplinary Palliative Care Education), provide valuable opportunities to develop such skills.

Accumulating evidence suggests that palliative care consultation programs are associated with significant hospital cost savings. Although data are lacking with respect to the health care expenditures for the early integration of palliative care into standard oncology care, the comanagement model has the potential to improve resource use by addressing patients’ symptoms immediately and collaboratively as they emerge, ideally reducing the likelihood of excessive procedures, emergency department visits, and acute hospital stays. For example, Brumley et al observed fewer emergency department visits and hospital admissions, as well as lower costs of care, with use of an in-home palliative care intervention. At a minimum, early palliative care appears to assist patients and families with making difficult decisions about treatment at the end of life, minimizing the potentially harmful effects and high costs of near-death chemotherapy while maximizing quality of life.

Conclusions

Although a number of studies have supported the feasibility and particular benefits of various aspects of palliative care, especially in promoting patient and family satisfaction with care, methodological weaknesses have limited conclusions about the overall usefulness of such programs to alleviate symptoms and improve quality of life. Overcoming many of the problems of prior research, two recently published randomized controlled trials have offered the best evidence to date regarding the efficacy of early palliative care interventions delivered concurrently with oncology care for patients with advanced cancer. Thus, introducing palliative care services soon after diagnosis for patients with advanced cancer helps to enhance quality of life, reduce depression, improve the quality of care at the end of life, and possibly prolong survival (ie, in the case of those with metastatic NSCLC). Further research is needed to elucidate the mechanisms by which palliative care interventions lead to these effects, as well as to adapt and apply novel models of early palliative care in the full continuum of care settings (home, office, cancer center, nursing home, and hospital). Nonetheless, the delivery of integrated palliative and oncology care services throughout the course of advanced cancer improves multiple outcomes for patients and families while simultaneously achieving the highest caliber of comprehensive cancer care.

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