# Effects of Early Integrated Palliative Care on Caregivers of Patients with Lung and Gastrointestinal Cancer: A Randomized Clinical Trial

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*Disclosures of potential conflicts of interest may be found at the end of this article.*

## Abstract

**Background.** The family and friends (caregivers) of patients with advanced cancer often experience tremendous distress. Although early integrated palliative care (PC) has been shown to improve patient-reported quality of life (QOL) and mood, its effects on caregivers' outcomes is currently unknown.

**Materials and Methods.** We conducted a randomized trial of early PC integrated with oncology care versus oncology care alone for patients who were newly diagnosed with incurable lung and noncolorectal gastrointestinal cancers and their caregivers. The early PC intervention focused on addressing the needs of both patients and their caregivers. Eligible caregivers were family or friends who would likely accompany patients to clinic visits. The intervention entailed at least monthly patient visits with PC from the time of diagnosis. Caregivers were encouraged, but not required, to attend the palliative care visits. We used the Hospital Anxiety and Depression Scale (HADS) and Medical Health Outcomes Survey Short-Form to assess caregiver mood and QOL.

**Results.** Two hundred seventy-five caregivers (intervention $n = 137$; control $n = 138$) of the 350 patients participated. The intervention led to improvement in caregivers' total distress (HADS-total adjusted mean difference = $-1.45$, 95% confidence interval [CI] $-2.76$ to $-0.15$, $p = .029$), depression subscale (HADS-depression adjusted mean difference = $-0.71$, 95% CI $-1.38$ to $-0.05$, $p = .036$), but not anxiety subscale or QOL at week 12. There were no differences in caregivers' outcomes at week 24. A terminal decline analysis showed significant intervention effects on caregivers' total distress (HADS-total), with effects on both the anxiety and depression subscales at 3 and 6 months before patient death.

**Conclusion.** Early involvement of PC for patients with newly diagnosed lung and gastrointestinal cancers leads to improvement in caregivers' psychological symptoms. This work demonstrates that the benefits of early, integrated PC models in oncology care extend beyond patient outcomes and positively impact the experience of caregivers. *The Oncologist* 2017;22:1528–1534

**Implications for Practice:** Early involvement of palliative care for patients with newly diagnosed lung and gastrointestinal cancers leads to improvement in caregivers' psychological symptoms. The findings of this trial demonstrate that the benefits of the early, integrated palliative care model in oncology care extend beyond patient outcomes and positively impact the experience of caregivers. These findings contribute novel data to the growing evidence base supporting the benefits of integrating palliative care earlier in the course of disease for patients with advanced cancer and their caregivers.

## Introduction

Family and friends (caregivers) play a critical role in providing care for patients with advanced cancer [1, 2]. Caring for a loved one with cancer requires considerable stamina [3, 4] and often results in substantial burden that negatively impacts caregivers' quality of life (QOL) and mood [5]. In fact, caregivers experience psychological distress that at times exceeds the psychological burden of patients with cancer [6, 7], underscoring the need to address caregivers' psychosocial well-being [8]. Because caregivers provide the majority of care for patients with cancer, attending to their psychological needs is also key to ensuring the delivery of high-quality care for patients with advanced cancer [9].

Early integration of specialty palliative care (PC) with oncology care for patients with advanced cancer improves a wide

range of patient outcomes, including symptom burden, QOL, depression, and illness understanding [10–13]. Notably, PC clinicians view supporting patients' caregivers as an essential aspect of their practice, including addressing caregivers' concerns and helping them cope effectively with their loved ones' illness [14]. Consequently, PC clinicians may reduce caregivers' distress by enhancing their coping skills and providing them with effective self-care strategies [14]. The American Society of Clinical Oncology (ASCO) recently released a Clinical Practice Guideline recommending concurrent PC from the time of diagnosis for all patients with metastatic cancer and their caregivers [15]. Thus, it is important that we describe the potential benefits of early palliative care on caregiver outcomes.

Prior studies have examined the effect of caregiver-directed psychological and PC-based psychoeducational interventions on caregiver QOL and mood [16, 17]. The ENABLE III trial compared an early versus delayed caregiver-directed, PC-based psychoeducational intervention, demonstrating improvements in caregivers' depression and stress burden [16]. However, other PC studies have not specifically included a caregiver-directed intervention, but rather focused on the potential impact of the integration of specialty-trained PC clinicians on the care of patients with advanced cancer and their caregivers collectively [13, 18, 19]. In a recent study, the integration of specialty-trained PC clinicians in the care of patients with poor-prognosis advanced cancer led to an increase in caregiver satisfaction with care, without a significant effect on their QOL [18]. However, this study did not examine early integrated PC from the time of diagnosis of advanced cancer as recommended by the ASCO Clinical Practice Guidelines. Therefore, studies are still needed to fully explore the potential benefits of the early integrated PC model on caregiver outcomes.

We conducted a single-center, randomized clinical trial to evaluate the effect of early integrated PC on patient- and caregiver-reported outcomes in patients with newly diagnosed, incurable cancers. We hypothesized that caregivers of patients assigned to early integrated PC would report lower psychological distress and better QOL compared with caregivers of patients assigned to usual oncology care.

## Materials and Methods

### Study Design
We conducted a randomized, nonblinded clinical trial of early PC integrated with oncology care versus usual oncology care for patients with newly diagnosed incurable lung or noncolorectal gastrointestinal (GI) cancers and their caregivers [19]. The study was conducted at the Massachusetts General Hospital (MGH) and approved by the Institutional Review Board.

### Study Participants
Patient eligibility criteria included the following: (a) aged ≥18 years; (b) diagnosis of incurable lung (non-small cell, small cell, or mesothelioma) or noncolorectal GI (pancreatic, esophageal, gastric, or hepatobiliary) cancer within the past 8 weeks; (c) receiving cancer care at MGH; (d) no prior therapy for metastatic disease; (e) an Eastern Cooperative Oncology Group performance status of 0–2; and (f) ability to respond to questions in English or complete questionnaires with minimal assistance from an interpreter. We excluded patients who were already

receiving PC services, needed immediate referral for PC or hospice, or had significant psychiatric or other comorbid disease prohibiting participation.

Upon enrollment, patients were asked to identify a caregiver who could be invited to participate in the study. Patients without a caregiver were still able to participate. Patients were asked to identify a relative or a friend who would likely accompany them to clinic visits. In addition, caregivers were required to be at least 18 years old and to have the ability to respond to questions in English or complete questionnaires with minimal assistance from an interpreter.

Study staff screened consecutively eligible patients presenting to the MGH oncology clinics and notified oncology clinicians via email when patients were eligible for the study. At the time of visit, study staff placed a reminder about eligibility on the patients' charts. Oncology clinicians then invited patients and their caregivers to enroll in the study. Willing patients and caregivers provided written informed consent. Caregivers were eligible to enroll and complete baseline data collection within 1 month of the patient's informed consent.

### Randomization
After obtaining informed consent, patients and their caregivers were randomly assigned to receive either early integrated palliative and oncology care or usual oncology care. Participants were randomized in a 1:1 fashion, stratified by cancer type, by the Office of Data Quality using a computer-generated number sequence, which was concealed until after group assignment. The Office of Data Quality was responsible for participants' registration and assignment to the study groups, but did not have any involvement in the rest of the trial. Patients, caregivers, oncology and PC clinicians, and study investigators were not blinded to the group assignment.

### Study Procedures
Patients assigned to early PC met with a board-certified PC physician or advanced-practice nurse within 4 weeks of enrollment and at least monthly until death. Caregivers were encouraged, but not required, to attend the PC visits. Palliative care clinicians could also contact intervention patients via telephone when an in-person visit was not possible. The patient, caregiver, oncologist, or PC clinician could schedule additional PC visits at their discretion. For patients admitted to the MGH, the inpatient PC team followed them during their hospitalization.

The main areas of focus of the PC intervention visits were reported previously [19]. After each study encounter, the PC clinicians documented the topics covered during the visit: addressing patients' symptoms, enhancing coping efforts, establishing rapport, illness and prognostic understanding, assisting with treatment decisions, advance care planning, and discussing disposition [19]. Palliative care clinicians engaged both patients and caregivers when addressing these topics. The mean number of PC visits by 24 weeks was 6.54 (range 0–14) in the intervention group.

Patients assigned to usual oncology care were able to meet with a PC clinician only upon request by the oncologist, patient, or caregiver. When these patients received PC services, they did not cross over to the intervention group. The PC team met with 20.0% and 34.3% of usual care patients by weeks 12 and 24, respectively. Otherwise, all study patients, regardless of group assignment, continued to receive routine oncology care.
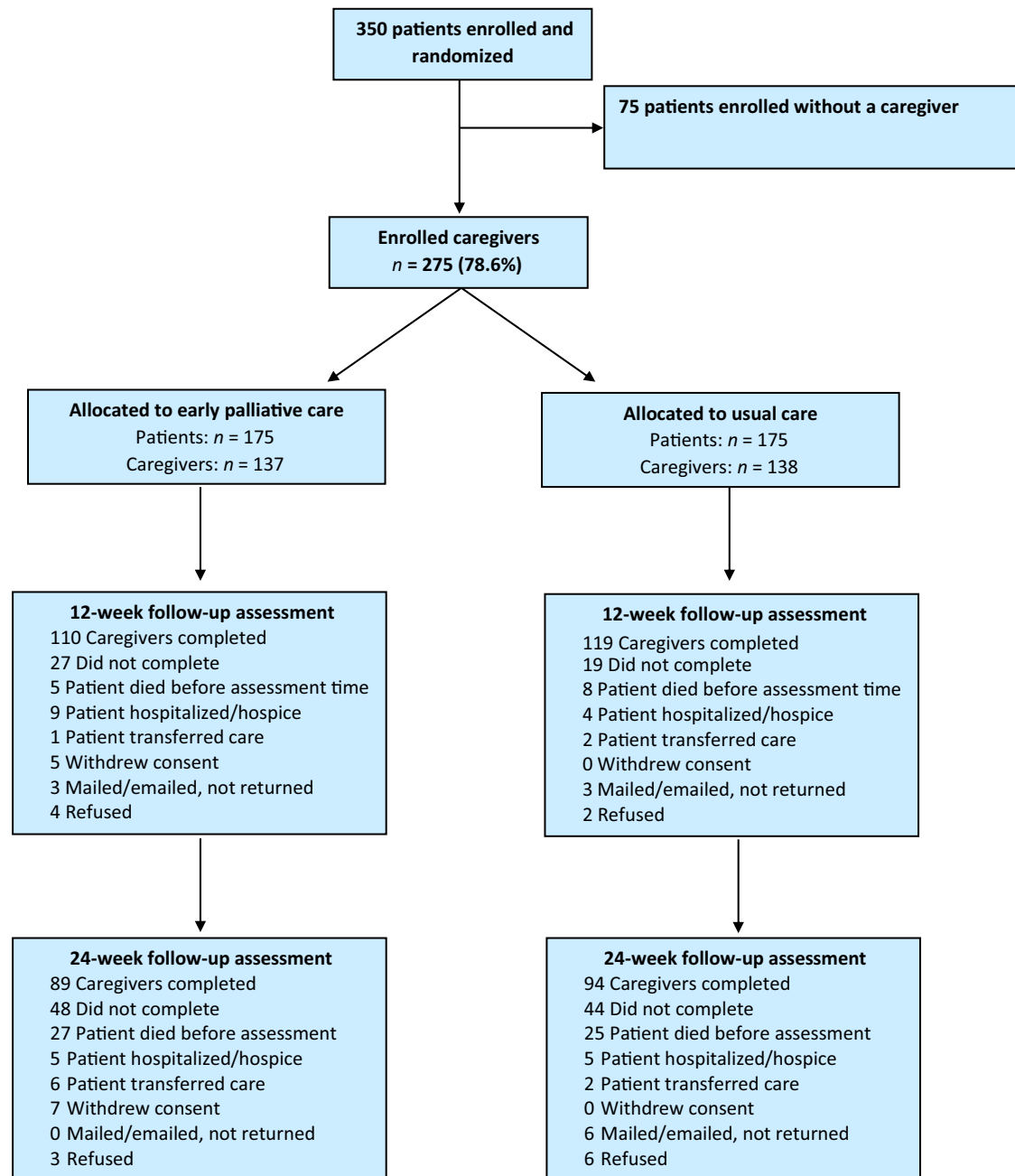
**Figure 1.** Consort diagram.

## Caregiver-Reported Outcome Measures

To assess mood and anxiety symptoms, caregivers completed the Hospital Anxiety and Depression Scale (HADS). The 14-item HADS consists of 2 subscales assessing anxiety and depression symptoms in the past week. Subscale scores on the HADS range from 0 (no distress) to 21 (maximum distress). The HADS can also yield a total sum score indicating the degree of psychological distress. Both HADS-total score and depression and anxiety subscale scores have been utilized in prior studies [20–23]. We measured caregiver QOL with the Medical Health Outcomes Survey-Short Form (SF-36) [24]. The SF-36 measures eight domains of health-related QOL and response choices are scored and summed to yield two physical (PCS) and mental (MCS) component summary measures. The SF-36 possesses

strong psychometric properties and is appropriate for caregivers because it does not target a specific population, age, or disease state.

## Data Collection

Caregivers completed a demographic questionnaire and baseline self-report measures after providing written informed consent, as well as follow-up assessments at 12 and 24 weeks (± 3-week window). Cancer Center protocol staff, separate from the research team, administered study questionnaires. Caregivers who did not attend patients' scheduled clinic visits within the designated time frames, or who were unable to complete questionnaires in clinic, received the questionnaires by secure email or mail.

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## Statistical Analysis

We performed statistical analyses using STATA (v9.3; StataCorp LLC, College Station, TX, http://www.stata.com) and R (v3.3.1; open-source software, https://www.r-project.org). Data obtained through May 2016 were included. All participants' characteristics and outcomes were summarized as frequency and percentage for categorical variables and mean ± standard deviation (SD) for continuous variables. The study was powered for the primary outcome of change in patient-reported QOL [19], but not the secondary caregiver outcomes.

We first used analysis of covariance models controlling for baseline criterion scores to examine caregiver psychological distress and QOL at weeks 12 and 24 based on available cases without accounting for missing data. Then, using a terminal decline joint modeling approach, we also compared caregiver-reported outcomes between the intervention and control groups at 3 and 6 months prior to death [25]. The terminal decline joint modeling approach was not prespecified in our protocol statistical analyses because it was first published in 2013 after the initiation of the study. However, this modeling technique offers a particularly advantageous approach to account for the dependence between patient- and caregiver-reported outcomes and patients' survival in PC studies while accounting for missing data [16, 25, 26]. The advantage of this method is that it models the trend in caregiver-reported outcomes backward from the time of the patients' death rather than prospectively from the time of enrollment. Thus, this approach controls for the known relationship between patient and caregiver QOL deterioration as patients' death approaches [25, 27–29]. Notably, the terminal decline joint-modeling approach also accounts for missing outcome data by utilizing a mixed-effects model for the longitudinal outcomes to provide valid and efficient estimates for missing data. We estimated terminal decline and survival distributions with semiparametric models to allow flexible nonlinear longitudinal trajectories in both the intervention and control group. On the basis of the fitted models, we compared caregiver-reported psychological outcomes and QOL at specified times before death (3 and 6 months prior to patient's death). All models adjusted for baseline criterion scores. This joint-modeling approach utilizes data from all caregivers ($n = 275$) and accounts for censored survival times because it estimates the survival distribution based on the survival data from all patients (regardless of whether they die or did not die in the study), and simultaneously uses this survival distribution to infer the terminal decline or trajectory of caregiver-reported outcomes.

## RESULTS

### Baseline Characteristics

A total of 350 patients enrolled in the study between May 2, 2011, and July 20, 2015, and 78.6% ($n = 275$) of patients identified a caregiver who agreed to participate in the study (Fig. 1). Enrolled caregivers were mostly female (190/275, 69.1%), married to the patient (184/275, 66.9%), and with a mean age of 57.4 (SD = 13.6) years (Table 1). There were no meaningful differences in caregiver characteristics between study groups at baseline. Overall, 229 and 183 caregivers completed the week 12 and week 24 assessments with a missing data rate of 16.7% and 33.5%, respectively. Among all 2,862 PC visits in the

intervention group, 71.6% (2049/2862) were attended by any caregiver (caregivers enrolled in the study were not required to attend visits). The median number of PC visits attended by caregivers was 10 (range 1–51). By January 20, 2016 (24-week follow-up for all participants), 272/350 (77.7%) of patients had died.

### Caregiver Psychological Outcomes and QOL

At week 12, caregivers in the intervention group reported significantly lower total psychological distress as measured by

**Table 1.** Caregivers' baseline characteristics

| Caregiver characteristics | Usual care ($n = 138$) n (%) | Palliative care ($n = 137$) n (%) |
|---|---|---|
| Age, mean (SD) | 57.2 (12.5) | 57.5 (14.7) |
| Gender | | |
| Male | 42 (30.4) | 43 (31.4) |
| Female | 96 (69.6) | 94 (68.6) |
| Race | | |
| White | 128 (92.8) | 127 (92.7) |
| American Indian | 1 (0.72) | 0 |
| Asian | 4 (2.9) | 4 (2.9) |
| Black | 2 (1.5) | 3 (2.2) |
| Hispanic | 3 (2.2) | 2 (1.5) |
| Other | 0 | 1 (0.73) |
| Hispanic ethnicity | 3 (2.3) | 5 (3.9) |
| Religion | | |
| Catholic | 81 (58.7) | 80 (58.4) |
| Protestant | 28 (20.3) | 17 (12.4) |
| Jewish | 2 (1.4) | 9 (6.6) |
| Muslim | 1 (0.72) | 1 (0.73) |
| None | 12 (8.7) | 15 (11.0) |
| Other | 13 (9.5) | 15 (11.0) |
| Missing | 1 (0.72) | 0 |
| Relationship to the patient | | |
| Married/partner | 92 (66.7) | 92 (67.2) |
| Child | 22 (15.9) | 29 (21.2) |
| Parent | 6 (4.4) | 0 |
| Sibling | 11 (8.0) | 1 (0.74) |
| Friend | 3 (2.2) | 9 (6.6) |
| Other | 4 (2.9) | 5 (3.7) |
| Missing | 0 | 1 (0.73) |
| Education | | |
| High school | 47 (34.1) | 26 (19.0) |
| College | 63 (45.7) | 75 (54.7) |
| Graduate school | 28 (20.3) | 35 (25.5) |
| Missing | 0 | 1 (0.7) |
| Employment | | |
| Working | 69 (50.0) | 74 (54.0) |
| Not working | 62 (44.9) | 59 (43.1) |
| Missing | 7 (5.1) | 4 (2.9) |

Abbreviation: SD, standard deviation.

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**Table 2.** Effect of early integrated palliative care on caregivers' outcomes at 12 and 24 weeks

| | Sample size | Group assignment | Adjusted mean score | 95% CI | Adjusted mean difference | 95% CI | Effect size d | p value |
|---|---|---|---|---|---|---|---|---|
| **Week 12 outcomes[a]** | | | | | | | | |
| HADS-Total distress | n = 227 | Control<br>Intervention | 10.48<br>9.02 | 9.58–11.38<br>8.09–9.96 | −1.45 | −2.76 to −0.15 | 0.300 | **.029** |
| SF-36 PCS | n = 228 | Control<br>Intervention | 51.40<br>52.94 | 49.83–52.98<br>51.30–54.59 | 1.54 | −0.74–3.82 | 0.180 | .183 |
| SF-36 MCS | n = 228 | Control<br>Intervention | 45.92<br>47.00 | 44.25–47.59<br>45.26–48.74 | 1.09 | −1.33–3.51 | 0.119 | .376 |
| **Week 24 outcomes[a]** | | | | | | | | |
| HADS-Total distress | n = 180 | Control<br>Intervention | 10.72<br>9.82 | 9.60–11.84<br>8.65–10.99 | −0.89 | −2.51–0.73 | 0.145 | .279 |
| SF-36 PCS | n = 179 | Control<br>Intervention | 53.22<br>52.71 | 51.58–54.86<br>51.02–54.40 | −0.51 | −2.87–1.85 | 0.057 | .669 |
| SF-36 MCS | n = 179 | Control<br>Intervention | 45.59<br>46.21 | 43.53–47.65<br>44.09–48.33 | 0.62 | −2.33–3.57 | 0.060 | .679 |

[a]Results of ANCOVA models controlling for baseline values for the criterion outcome.
Bolded p-values are statistically significant.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; HADS, hospital anxiety and depression scale, higher scores indicate higher distress; SF-36 PCS, Medical Outcomes Health Questionnaire Short Form (SF-36) physical component score; SF-36 MCS, Medical Outcomes Health Questionnaire Short Form (SF-36) mental component score, higher scores indicate better quality of life.

**Table 3.** Effect of early integrated palliative care on caregivers' outcomes at 3 and 6 months prior to death

| | 3 months before death | | | 6 months before death | | |
|---|---|---|---|---|---|---|
| **Entire sample[a]** | Mean | (95% CI) | p value | Mean | (95% CI) | p value |
| HADS-Total distress | | | .002 | | | .003 |
|   Early palliative care | 6.84 | (4.11–9.58) | | 7.88 | (6.16–9.61) | |
|   Usual care | 12.93 | (10.28–15.59) | | 11.60 | (9.89–13.31) | |
| SF-36 PCS | | | .664 | | | .299 |
|   Early palliative care | 52.69 | (51.00–54.38) | | 53.27 | (51.71–54.83) | |
|   Usual care | 52.17 | 50.56–53.57 | | 52.14 | (50.67–53.61) | |
| SF-36 MCS | | | .579 | | | .338 |
|   Early palliative care | 46.75 | (44.88–48.62) | | 47.10 | (45.33–48.87) | |
|   Usual care | 46.01 | (44.23–47.80) | | 45.91 | (44.25–47.57) | |

[a]Results of terminal decline models controlling for baseline values for the criterion outcome.
Bolded p-values are statistically significant.
Abbreviations: CI, confidence interval; HADS, hospital anxiety and depression scale, higher scores indicate higher distress; SF-36 PCS, Medical Outcomes Health Questionnaire Short Form (SF-36) physical component score; SF-36 MCS, Medical Outcomes Health Questionnaire Short Form (SF-36) mental component score, higher scores indicate better quality of life.

HADS-total score (adjusted mean difference = −1.45, 95% CI −2.76 to −0.15, p = .029). When examining HADS subscale scores, caregivers in the intervention group reported lower depression subscale scores (adjusted mean difference = −0.71, 95% CI −1.38 to −0.05, p = .036), but not anxiety symptoms (adjusted mean difference = −0.73, 95% CI −1.57 to 0.11, p = .089) compared with caregivers in the controlgroups at 12 weeks.

Using all available data, we observed no significant intervention effects on caregivers' total psychological distress, depression or anxiety subscales, or QOL (SF-36) at week 24. However, using the terminal decline model to account for missing data and deterioration in caregivers' outcomes closer to death, caregivers in the intervention group reported significantly lower total psychological distress (HADS-total), with lower depression and anxiety symptoms subscales, compared with caregivers in the control group at 3 and 6 months prior to the patients' death (Table 3). Caregiver-reported QOL as measured by the SF-36 did not differ between the two groups at 3 and 6 months prior to death.

## Discussion

The findings of this trial demonstrate that the benefits of the early, integrated PC model in oncology care extend beyond patient outcomes and positively impact the experience of caregivers. Specifically, the caregivers of patients assigned to early PC reported lower depression symptoms, as well as less anxiety in the months closer to the patients' death compared with caregivers of patients assigned to usual oncology care. These findings contribute novel data to the growing evidence base supporting the benefits of integrating PC earlier in the course of disease for patients with advanced cancer and their caregivers.

To our knowledge, this is the first study demonstrating the beneficial effects of having PC clinicians integrated early in the clinical care of patients with advanced cancer on caregivers' psychological distress. Our systematic screening procedures, along with having the oncology clinicians offer trial participation for both patients and caregivers, likely led to relatively high participation rates. Prior trials of caregiver-directed psychological interventions in oncology have shown only marginal

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benefits on caregiver psychological distress without significant impact on QOL [16, 17, 30]. In contrast, ENABLE III demonstrated improvement in caregivers' depression and stress burden with a caregiver-directed intervention [16], but it did not examine the effect of an early integrated PC intervention targeting the needs of both patients and caregivers collectively, as proposed by the ASCO Clinical Practice Guidelines [15]. A recent study demonstrated that the integration of specialty-trained PC clinicians in the care of patients with poor-prognosis advanced cancer led to an increase in caregiver satisfaction with care [18], but it did not examine the effect of PC integration early in the course of illness or its impact on caregivers' psychological distress [18]. Thus, our findings are particularly relevant because they highlight the benefits of the early integrated specialty PC model, which is becoming the standard of care for patients with advanced cancer [31].

Although we noted improvement in caregivers' psychological distress, the mechanism by which early integrated PC impacts caregivers' outcomes remain unknown. Caregivers may have benefited from their direct interaction with the PC clinicians. Alternatively, improvement in patient-reported outcomes with early integrated PC may have led to a reduction in caregivers' psychological distress. Future studies should be adequately powered to better assess potential mediators of the effect of early integrated PC on caregiver outcomes given the critical role that they play in providing care and support for patients with advanced cancer.

We noted significant intervention effects on caregiver psychological outcomes at 12 weeks, but not at the 24-week assessment. This discrepancy is likely due to the lack of statistical power to detect meaningful differences in outcomes at 24 weeks using available case analyses, given the rate of missing data at 24 weeks was 33.5%. Attrition rates are always problematic in PC studies, further complicating the interpretations of study findings [32]. However, when using terminal decline analyses, which account for missing data, we observed significant intervention effects on caregiver depression and anxiety symptoms 3 and 6 months prior to the patient's death. Ideally, future studies should be adequately powered to assess the longitudinal impact of PC integration on caregiver outcomes throughout the patient's illness course.

Although early PC improved caregivers' psychological outcomes, we did not detect an effect on their QOL. Prior caregiver interventions in oncology have also failed to enhance QOL [18, 33]. Interestingly, the SF-36 PCS scores among caregivers enrolled in our study were slightly better than the general population norm [24, 34]. Therefore, it is possible that a general QOL assessment may not appropriately capture the impact of these interventions on caregivers' experience. Rather, closer attention must be paid to utilizing instruments that comprehensively assess domains of caregiving burden, stress, and burnout, as well as psychological outcomes.

Our study has several important limitations. First, we conducted the trial at a single cancer center, which may limit the generalizability of the results to other care settings and clinical populations. Second, patients, caregivers, and clinicians could not be blinded to the intervention, which may have introduced bias. Third, because the caregiver outcomes were secondary endpoints in this trial, the study may have lacked adequate statistical power to fully assess the effect of the intervention on caregiver outcomes. In addition, caregivers were encouraged, although not required, to attend the PC visits with patients, which may have diminished the potential impact of the intervention. Finally, because usual care at our institution often entails involvement of PC in the outpatient setting, a proportion of patients and caregivers assigned to usual care met with the PC team during the study. This contact may have also diluted the effect of the intervention.

## CONCLUSION

Early integration of palliative and oncology care in patients with newly diagnosed incurable cancer reduces caregivers' depression and lowers their anxiety in the months prior to the patient's death. These findings provide critical evidence to support the role of early integrated PC in enhancing the experience of caregivers of patients with newly diagnosed incurable cancers. As cancer care continues to evolve and extend the lives of patients with incurable cancers, the role of caregivers in supporting their loved ones will continue to expand. Early integrated palliative care is a novel, efficacious approach to support these patients and families.

## AUTHOR CONTRIBUTIONS

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