

ORIGINAL ARTICLE

Early Palliative Care for Patients with Metastatic Non–Small-Cell Lung Cancer

Jennifer S. Temel, M.D., Joseph A. Greer, Ph.D., Alona Muzikansky, M.A.,
Emily R. Gallagher, R.N., Sonal Admane, M.B., B.S., M.P.H.,
Vicki A. Jackson, M.D., M.P.H., Constance M. Dahlin, A.P.N.,
Craig D. Blinderman, M.D., Juliet Jacobsen, M.D., William F. Pirl, M.D., M.P.H.,
J. Andrew Billings, M.D., and Thomas J. Lynch, M.D.

ABSTRACT

BACKGROUND

Patients with metastatic non–small-cell lung cancer have a substantial symptom burden and may receive aggressive care at the end of life. We examined the effect of introducing palliative care early after diagnosis on patient-reported outcomes and end-of-life care among ambulatory patients with newly diagnosed disease.

METHODS

We randomly assigned patients with newly diagnosed metastatic non–small-cell lung cancer to receive either early palliative care integrated with standard oncologic care or standard oncologic care alone. Quality of life and mood were assessed at baseline and at 12 weeks with the use of the Functional Assessment of Cancer Therapy–Lung (FACT-L) scale and the Hospital Anxiety and Depression Scale, respectively. The primary outcome was the change in the quality of life at 12 weeks. Data on end-of-life care were collected from electronic medical records.

RESULTS

Of the 151 patients who underwent randomization, 27 died by 12 weeks and 107 (86% of the remaining patients) completed assessments. Patients assigned to early palliative care had a better quality of life than did patients assigned to standard care (mean score on the FACT-L scale [in which scores range from 0 to 136, with higher scores indicating better quality of life], 98.0 vs. 91.5; $P=0.03$). In addition, fewer patients in the palliative care group than in the standard care group had depressive symptoms (16% vs. 38%, $P=0.01$). Despite the fact that fewer patients in the early palliative care group than in the standard care group received aggressive end-of-life care (33% vs. 54%, $P=0.05$), median survival was longer among patients receiving early palliative care (11.6 months vs. 8.9 months, $P=0.02$).

CONCLUSIONS

Among patients with metastatic non–small-cell lung cancer, early palliative care led to significant improvements in both quality of life and mood. As compared with patients receiving standard care, patients receiving early palliative care had less aggressive care at the end of life but longer survival. (Funded by an American Society of Clinical Oncology Career Development Award and philanthropic gifts; ClinicalTrials.gov number, NCT01038271.)

From Massachusetts General Hospital, Boston (J.S.T., J.A.G., A.M., E.R.G., V.A.J., C.M.D., J.J., W.F.P., J.A.B.); the State University of New York, Buffalo (S.A.); Adult Palliative Medicine, Department of Anesthesiology, Columbia University Medical Center, New York (C.D.B.); and Yale University, New Haven, CT (T.J.L.). Address reprint requests to Dr. Temel at Massachusetts General Hospital, 55 Fruit St., Yawkey 7B, Boston, MA 02114, or at jtemel@partners.org.

N Engl J Med 2010;363:733-42.

Copyright © 2010 Massachusetts Medical Society.

THE QUALITY OF CARE AND THE USE OF medical services for seriously ill patients are key elements in the ongoing debate over reform of the U.S. health care system.¹ Oncologic care is central to this debate, largely because anticancer treatments are often intensive and costly.² Comprehensive oncologic services for patients with metastatic disease would ideally improve the patients' quality of life and facilitate the efficient allocation of medical resources. Palliative care, with its focus on management of symptoms, psychosocial support, and assistance with decision making, has the potential to improve the quality of care and reduce the use of medical services.^{3,4} However, palliative care has traditionally been delivered late in the course of disease to patients who are hospitalized in specialized inpatient units or as a consultative service for patients with uncontrolled symptoms.^{5,6} Previous studies have suggested that late referrals to palliative care are inadequate to alter the quality and delivery of care provided to patients with cancer.^{7,8} To have a meaningful effect on patients' quality of life and end-of-life care, palliative care services must be provided earlier in the course of the disease.

Metastatic non–small-cell lung cancer, the leading cause of death from cancer worldwide,⁹ is a debilitating disease that results in a high burden of symptoms and poor quality of life; the estimated prognosis after the diagnosis has been established is less than 1 year.^{10–12} We previously found that introducing palliative care shortly after diagnosis was feasible and acceptable among outpatients with metastatic non–small-cell lung cancer.¹³ The goal of the current study was to examine the effect of early palliative care integrated with standard oncologic care on patient-reported outcomes, the use of health services, and the quality of end-of-life care among patients with metastatic non–small-cell lung cancer. We hypothesized that patients who received early palliative care in the ambulatory care setting, as compared with patients who received standard oncologic care, would have a better quality of life, lower rates of depressive symptoms, and less aggressive end-of-life care.

METHODS

STUDY DESIGN

From June 7, 2006, to July 15, 2009, we enrolled ambulatory patients with newly diagnosed meta-

static non–small-cell lung cancer in a nonblinded, randomized, controlled trial of early palliative care integrated with standard oncologic care, as compared with standard oncologic care alone. The study was performed at Massachusetts General Hospital in Boston. Eligible patients were enrolled within 8 weeks after diagnosis and were randomly assigned to one of the two groups in a 1:1 ratio without stratification. Patients who were assigned to early palliative care met with a member of the palliative care team, which consisted of board-certified palliative care physicians and advanced-practice nurses, within 3 weeks after enrollment and at least monthly thereafter in the outpatient setting until death. Additional visits with the palliative care service were scheduled at the discretion of the patient, oncologist, or palliative care provider.

General guidelines for the palliative care visits in the ambulatory setting were adapted from the National Consensus Project for Quality Palliative Care and were included in the study protocol.¹⁴ Using a template in the electronic medical record, palliative care clinicians documented the care they provided according to these guidelines (see Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Specific attention was paid to assessing physical and psychosocial symptoms, establishing goals of care, assisting with decision making regarding treatment, and coordinating care on the basis of the individual needs of the patient.^{14,15} Patients who were randomly assigned to standard care were not scheduled to meet with the palliative care service unless a meeting was requested by the patient, the family, or the oncologist; those who were referred to the service did not cross over to the palliative care group or follow the specified palliative care protocol. All the participants continued to receive routine oncologic care throughout the study period. Before enrollment in the study was initiated, the protocol was approved by the Dana Farber/Partners CancerCare institutional review board. All participants provided written informed consent. The protocol, including the statistical analysis plan, is available at NEJM.org. All the authors attest that the study was performed in accordance with the protocol and the statistical analysis plan.

PATIENTS

Patients who presented to the outpatient thoracic oncology clinic were invited by their medical on-

oncologists to enroll in the study; all the medical oncologists in the clinic agreed to approach, recruit, and obtain consent from their patients. Physicians were encouraged, but not required, to offer participation to all eligible patients; no additional screening or recruitment measures were used. Patients were eligible to participate if they had pathologically confirmed metastatic non-small-cell lung cancer diagnosed within the previous 8 weeks and an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (with 0 indicating that the patient is asymptomatic, 1 that the patient is symptomatic but fully ambulatory, and 2 that the patient is symptomatic and in bed <50% of the day)¹⁶ and were able to read and respond to questions in English. Patients who were already receiving care from the palliative care service were not eligible for participation in the study.

PATIENT-REPORTED MEASURES

Health-related quality of life was measured with the use of the Functional Assessment of Cancer Therapy–Lung (FACT-L) scale, which assesses multiple dimensions of the quality of life (physical, functional, emotional, and social well-being) during the previous week.¹⁷ In addition, the lung-cancer subscale (LCS) of the FACT-L scale evaluates seven symptoms specific to lung cancer. The primary outcome of the study was the change from baseline to 12 weeks in the score on the Trial Outcome Index (TOI), which is the sum of the scores on the LCS and the physical well-being and functional well-being subscales of the FACT-L scale.

Mood was assessed with the use of both the Hospital Anxiety and Depression Scale (HADS) and the Patient Health Questionnaire 9 (PHQ-9).^{18,19} The 14-item HADS, which consists of two subscales, screens for symptoms of anxiety and depression in the previous week. Subscale scores range from 0, indicating no distress, to 21, indicating maximum distress; a score higher than 7 on either HADS subscale is considered to be clinically significant. The PHQ-9 is a nine-item measure that evaluates symptoms of major depressive disorder according to the criteria of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV). A major depressive syndrome was diagnosed if a patient reported at least five of the nine symptoms of depression on the PHQ-9, with one of the five symptoms being either anhedonia or depressed mood. Symptoms

had to be present for more than half the time, except for the symptom of suicidal thoughts, which was included in the diagnosis if it was present at any time.

MEASURES OF HEALTH CARE USE

Data were collected from the electronic medical record on the use of health services and end-of-life care, including anticancer therapy, medication prescriptions, referral to hospice, hospital admissions, emergency department visits, and the date and location of death. Patients were classified as having received aggressive care if they met any of the following three criteria: chemotherapy within 14 days before death, no hospice care, or admission to hospice 3 days or less before death.²⁰⁻²² Finally, we assessed whether patients' resuscitation preferences were documented in the outpatient electronic medical record.²³

DATA COLLECTION

Participants completed baseline questionnaires before randomization. Follow-up assessments of quality of life and mood were performed at 12 weeks (or at an outpatient clinic visit within 3 weeks before or after that time point). Participants who had no scheduled clinic visits within this period received the questionnaires by mail. When responses on questionnaires were incomplete, research staff documented the reasons for which the participant did not give a full response.

STATISTICAL ANALYSIS

Data obtained through December 1, 2009, were included in the analyses. The primary outcome was the change in the score on the TOI from baseline to 12 weeks. We estimated that with 120 patients, the study would have 80% power to detect a significant between-group difference in the change in the TOI score from baseline to 12 weeks, with a medium effect size of 0.5 SD.²⁴ The protocol was amended in August 2008 to allow for the enrollment of an additional 30 participants in order to compensate for the loss of any patients to follow-up.

Statistical analyses were performed with the use of SPSS software, version 16.0 (SPSS). Descriptive statistics were used to estimate the frequencies, means, and standard deviations of the study variables. Differences between study groups in baseline characteristics and clinical outcomes were assessed with the use of two-sided Fisher's exact tests and chi-square tests for categorical

variables and independent-samples Student's t-tests for continuous variables. Multivariate linear regression analyses, adjusted for baseline scores, were used to examine the effect of early palliative care on quality-of-life outcomes. For intention-to-treat analyses, we used the conservative method of carrying baseline values forward to account for all missing patient-reported outcome data, including data that were missing owing to death. Survival time was calculated from the date of enrollment to the date of death with the use of the Kaplan–Meier method. Data from patients who were alive at the last follow-up (December 1,

2009) were censored on that date. A Cox proportional-hazards model was used to assess the effect of early palliative care on survival, with adjustment for demographic characteristics and baseline ECOG performance status.

RESULTS

BASELINE CHARACTERISTICS OF THE PATIENTS

A total of 151 patients were enrolled in the study (see the figure in the Supplementary Appendix). The percentage of patients enrolled was similar for each of the thoracic oncologists in the clinic.

Table 1. Baseline Characteristics of the Study Participants.*

Variable	Standard Care (N=74)	Early Palliative Care (N=77)	P Value†
Age — yr	64.87±9.41	64.98±9.73	0.94
Female sex — no. (%)	36 (49)	42 (55)	0.52
Race — no. (%)‡			0.06§
White	70 (95)	77 (100)	
Black	3 (4)	0	
Asian	1 (1)	0	
Hispanic or Latino ethnic group‡	1 (1)	1 (1)	1.00
Marital status — no. (%)			1.00
Married	45 (61)	48 (62)	
Single	9 (12)	9 (12)	
Divorced or separated	12 (16)	12 (16)	
Widowed	8 (11)	8 (10)	
ECOG performance status — no. (%)¶			0.24
0	30 (41)	26 (34)	
1	35 (47)	46 (60)	
2	9 (12)	5 (6)	
Presence of brain metastases — no. (%)	19 (26)	24 (31)	0.48
Initial anticancer therapy — no. (%)			0.87
Platinum-based combination chemotherapy	35 (47)	35 (45)	
Single agent	3 (4)	9 (12)	
Oral EGFR tyrosine kinase inhibitor	6 (8)	6 (8)	
Radiotherapy	26 (35)	27 (35)	
Chemoradiotherapy	3 (4)	0	
No chemotherapy	1 (1)	0	
Receipt of initial chemotherapy as part of a clinical trial — no. (%)	20 (27)	16 (21)	0.45
Never smoked or smoked ≤10 packs/yr — no./total no. (%)	16/73 (22)	18/76 (24)	0.85
Assessment of mood symptoms — no./total no. (%)			
HADS**			
Anxiety subscale	24/72 (33)	28/77 (36)	0.73
Depression subscale	18/72 (25)	17/77 (22)	0.70
PHQ-9 major depressive syndrome††	12/72 (17)	9/76 (12)	0.48

Table 1. (Continued.)

Variable	Standard Care (N=74)	Early Palliative Care (N=77)	P Value†‡
Scores on quality-of-life measures‡‡‡			
FACT-L scale	91.7±16.7	93.6±16.5	0.50
Lung-cancer subscale	18.7±4.4	20.1±4.4	
Trial Outcome Index	55.3±13.1	56.2±13.4	

- * Plus-minus values are means ±SD. Percentages may not total 100 because of rounding. ECOG denotes Eastern Cooperative Oncology Group, EGFR epidermal growth factor receptor, FACT-L Functional Assessment of Cancer Therapy–Lung, HADS Hospital Anxiety and Depression Scale, and PHQ-9 Patient Health Questionnaire 9.
- † P values were calculated with the use of two-sided chi-square and Fisher's exact tests for categorical variables and the independent-samples Student's t-tests for continuous variables.
- ‡ Race or ethnic group was self-reported.
- § The P value is for the between-group comparison of the proportions of patients who were white and those who were members of a minority group (black and Asian), calculated with the use of Fisher's exact test.
- ¶ An ECOG performance status of 0 indicates that the patient is asymptomatic, 1 that the patient is symptomatic but fully ambulatory, and 2 that the patient is symptomatic and in bed less than 50% of the day.
- || The P value is for the between-group comparison of the proportion of patients receiving platinum-based combination chemotherapy and the proportion receiving other treatments, calculated with the use of Fisher's exact test.
- ** The HADS consists of two subscales, one for symptoms of anxiety and one for symptoms of depression. Subscale scores range from 0, indicating no distress, to 21, indicating maximum distress; a score higher than 7 indicates clinically meaningful anxiety or depression.
- †† The PHQ-9 is a nine-item measure that evaluates symptoms of major depressive disorder according to the criteria of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. A major depressive syndrome was diagnosed if a patient reported at least five of the nine symptoms of depression on the PHQ-9, with one of the five symptoms being either anhedonia or depressed mood. Symptoms had to be present for more than half the time, except for the symptom of suicidal thoughts, which was included in the diagnosis if it was present at any time.
- ‡‡ The quality of life was assessed with the use of three measures: the FACT-L scale, on which scores range from 0 to 136, with higher scores indicating a better quality of life; the lung-cancer subscale of the FACT-L scale, on which scores range from 0 to 28, with higher scores indicating fewer symptoms; and the Trial Outcome Index, which is the sum of the scores on the lung-cancer, physical well-being, and functional well-being subscales of the FACT-L scale (scores range from 0 to 84, with higher scores indicating a better quality of life).

No significant differences in demographic characteristics or overall survival were seen between the study participants and eligible patients who were not enrolled in the study. The baseline characteristics were well matched between the two study groups (Table 1). Known prognostic factors, including age, sex, ECOG performance status, presence or absence of brain metastases, smoking status, and initial anticancer therapy, were also balanced between the study groups. Although genetic testing was not routinely performed, the proportions of patients with mutations in the epidermal growth factor gene (*EGFR*) were similar between the study groups among the patients who underwent testing (9% in the palliative care group and 12% in the standard-treatment group, $P=0.76$). No significant between-group differences were seen in baseline quality of life or mood symptoms.

PALLIATIVE-CARE VISITS

All the patients assigned to early palliative care, except for one patient who died within 2 weeks after enrollment, had at least one visit with the

palliative care service by the 12th week. The average number of visits in the palliative care group was 4 (range, 0 to 8). Ten patients who received standard care (14%) had a palliative care consultation in the first 12 weeks of the study, primarily to address the management of symptoms, with seven patients having one visit and three having two visits.

QUALITY-OF-LIFE AND MOOD OUTCOMES

A comparison of measures of quality of life at 12 weeks showed that the patients assigned to early palliative care had significantly higher scores than did those assigned to standard care, for the total FACT-L scale, the LCS, and the TOI, with effect sizes in the medium range (Table 2). Patients in the palliative care group had a 2.3-point increase in mean TOI score from baseline to 12 weeks, as compared with a 2.3-point decrease in the standard care group ($P=0.04$) (Fig. 1). With the use of linear regression to control for baseline quality-of-life values, the group assignment significantly predicted scores at 12 weeks on the total FACT-L scale (adjusted difference in mean

Table 2. Bivariate Analyses of Quality-of-Life Outcomes at 12 Weeks.*

Variable	Standard Care (N=47)	Early Palliative Care (N=60)	Difference between Early Care and Standard Care (95% CI)	P Value†	Effect Size‡
FACT-L score	91.5±15.8	98.0±15.1	6.5 (0.5–12.4)	0.03	0.42
LCS score	19.3±4.2	21.0±3.9	1.7 (0.1–3.2)	0.04	0.41
TOI score	53.0±11.5	59.0±11.6	6.0 (1.5–10.4)	0.009	0.52

* Plus-minus values are means ±SD. Quality of life was assessed with the use of three scales: the Functional Assessment of Cancer Therapy–Lung (FACT-L) scale, on which scores range from 0 to 136, with higher scores indicating better quality of life; the lung-cancer subscale (LCS) of the FACT-L scale, on which scores range from 0 to 28, with higher scores indicating fewer symptoms; and the Trial Outcome Index (TOI), which is the sum of the scores on the LCS and the physical well-being and functional well-being subscales of the FACT-L scale (scores range from 0 to 84, with higher scores indicating better quality of life).

† The P value was calculated with the use of two-sided Student's t-tests for independent samples.

‡ The effect size was determined with the use of Cohen's d statistic, which is a measure of the difference between two means (in this case, the mean in the group assigned to early palliative care group minus the mean in the group assigned to standard care) divided by a standard deviation for the pooled data. According to the conventional classification, an effect size of 0.20 is small, 0.50 moderate, and 0.80 large.

[±SE] scores, 5.4±2.4; 95% confidence interval [CI], 0.7 to 10.0; P=0.03) and the TOI (adjusted difference in mean scores, 5.2±1.8; 95% CI, 1.6 to 8.9; P=0.005), but not on the LCS (adjusted difference in mean scores, 1.0±0.6; 95% CI, –0.2 to 2.3; P=0.12). In addition, the percentage of patients with depression at 12 weeks, as measured by the HADS and PHQ-9, was significantly lower in the palliative care group than in the standard care group, although the proportions of patients receiving new prescriptions for antidepressant drugs were similar in the two groups (approximately 18% in both groups, P=1.00) (Fig. 2). The percentage of patients with elevated scores for symptoms of anxiety did not differ significantly between the groups.

The figure in the Supplementary Appendix includes an explanation of missing data according to study group. There was no significant association between missing data on patient-reported outcomes at 12 weeks and any baseline characteristic (although there was a trend toward a significant association between missing data and assigned treatment [P=0.07]). When we carried the baseline scores of the participants forward for the missing data on patient-reported outcomes, all primary treatment effects were replicated with respect to quality of life (P=0.04 for the 12-week FACT-L score, P=0.01 for the 12-week LCS score, P=0.04 for the 12-week TOI score, and P=0.04 for the mean change from baseline to 12 weeks in the TOI score) and mood (P=0.04 for the comparison of patients with elevated scores on the HADS depression subscale, and P=0.02

for the comparison of patients with symptoms of major depression on the PHQ-9).

END-OF-LIFE CARE

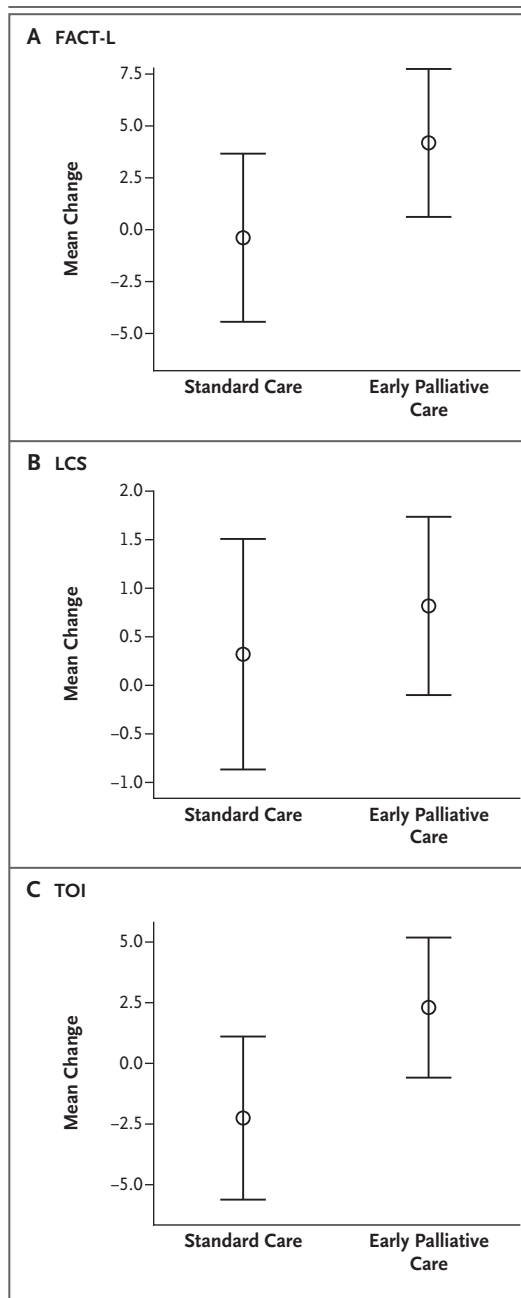
At the time of the analysis of end-of-life care, 105 participants (70%) had died; the median duration of follow-up among participants who died was 5.7 months. Within this subsample, a greater percentage of patients in the group assigned to standard care than in the group assigned to early palliative care received aggressive end-of-life care (54% [30 of 56 patients] vs. 33% [16 of 49 patients], P=0.05). In addition, fewer patients in the standard care group than in the palliative care group had resuscitation preferences documented in the outpatient electronic medical record (28% [11 of 39 patients who had preferences documented during the course of the study] vs. 53% [18 of 34 patients], P=0.05). The study did not have adequate power to examine specific indicators of aggressive care at the end of life. However, analyses of various measures of utilization, such as rates of hospitalization and emergency department visits (Table 2 in the Supplementary Appendix), as well as the duration of hospice care (median duration, 11 days in the palliative care group vs. 4 days in the standard care group; P=0.09 with the use of the Wilcoxon rank-sum test), suggested an improvement in the quality of care with early palliative care. Despite receiving less aggressive end-of-life care, patients in the palliative care group had significantly longer survival than those in the standard care group (median survival, 11.6 vs. 8.9 months; P=0.02) (Fig. 3).

Figure 1. Mean Change in Quality-of-Life Scores from Baseline to 12 Weeks in the Two Study Groups.

Quality of life was assessed with the use of the Functional Assessment of Cancer Therapy–Lung (FACT-L) scale, on which scores range from 0 to 136, with higher scores indicating a better quality of life; the lung-cancer subscale (LCS) of the FACT-L scale, on which scores range from 0 to 28, with higher scores indicating fewer symptoms; and the Trial Outcome Index (TOI), which is the sum of the scores on the LCS and the physical well-being and functional well-being subscales of the FACT-L scale (scores range from 0 to 84, with higher scores indicating a better quality of life). With study group as the independent variable, two-sided independent-samples Student's *t*-tests showed a trend toward a significant between-group difference in the mean (\pm SD) change in scores from baseline to week 12 on the FACT-L scale (-0.4 ± 13.8 in the standard care group vs. 4.2 ± 13.8 in the palliative care group; difference between groups, 4.6; 95% confidence interval [CI], -0.8 to 9.9; $P=0.09$) (Panel A), no significant between-group difference in the mean change in scores on the LCS (0.3 ± 4.0 and 0.8 ± 3.6 in the two groups, respectively; difference between groups, 0.5; 95% CI, -1.0 to 2.0; $P=0.50$) (Panel B), and a significant between-group difference in the mean change in scores on the TOI (-2.3 ± 11.4 vs. 2.3 ± 11.2 ; difference between groups, 4.6; 95% CI, 0.2 to 8.9; $P=0.04$) (Panel C). Data are from the 47 patients in the standard care group and the 60 patients in the palliative care group who completed the 12-week assessments. I bars indicate 95% confidence intervals.

DISCUSSION

This study shows the effect of palliative care when it is provided throughout the continuum of care for advanced lung cancer. Early integration of palliative care with standard oncologic care in patients with metastatic non–small-cell lung cancer resulted in survival that was prolonged by approximately 2 months and clinically meaningful improvements in quality of life and mood. Moreover, this care model resulted in greater documentation of resuscitation preferences in the outpatient electronic medical record, as well as less aggressive care at the end of life. Less aggressive end-of-life care did not adversely affect survival. Rather, patients receiving early palliative care, as compared with those receiving standard care alone, had improved survival. Previous data have shown that a lower quality of life and depressed mood are associated with shorter survival among patients with metastatic non–small-cell lung cancer.^{25–27} We hypothesize that improvements in both of these outcomes among patients assigned to early palliative care may ac-



count for the observed survival benefit. In addition, the integration of palliative care with standard oncologic care may facilitate the optimal and appropriate administration of anticancer therapy, especially during the final months of life. With earlier referral to a hospice program, patients may receive care that results in better management of symptoms, leading to stabilization of their condition and prolonged survival. These hypotheses require further study.

Improving quality of life and mood in patients

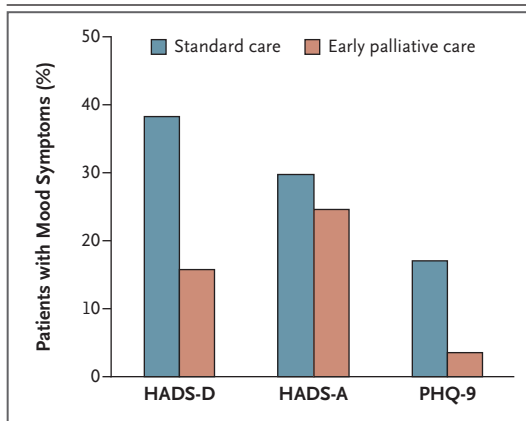


Figure 2. Twelve-Week Outcomes of Assessments of Mood.

Depressive symptoms were assessed with the use of the Hospital Anxiety and Depression Scale (HADS), which consists of two subscales, one for symptoms of anxiety (HADS-A) and one for symptoms of depression (HADS-D) (subscale scores range from 0, indicating no distress, to 21, indicating maximum distress; a score higher than 7 on either HADS subscale is considered to be clinically significant) and with the use of the Patient Health Questionnaire 9 (PHQ-9). The PHQ-9 is a nine-item measure that evaluates symptoms of major depressive disorder according to the criteria of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV). A major depressive syndrome was diagnosed if a patient reported at least five of the nine symptoms of depression on the PHQ-9, with one of the five symptoms being either anhedonia or depressed mood. Symptoms had to be present for more than half the time, except for the symptom of suicidal thoughts, which was included in the diagnosis if it was present at any time. The percentages of patients with mood symptoms, assessed on the basis of each of these measures, in the group assigned to standard treatment and the group assigned to early palliative care, respectively, are as follows: HADS-D, 38% (18 of 47 patients) versus 16% (9 of 57), $P=0.01$; HADS-A, 30% (14 of 47 patients) and 25% (14 of 57), respectively; $P=0.66$; and PHQ-9, 17% (8 of 47 patients) versus 4% (2 of 57); $P=0.04$. The analyses were performed with the use of a two-sided Fisher's exact test.

with metastatic non-small-cell lung cancer is a formidable challenge, given the progressive nature of the illness.²⁸ The improvement we observed in the quality of life among patients assigned to early palliative care, as indicated by a mean change in the TOI score by 12 weeks that was approximately 5 points higher in the palliative care group than in the standard care group, is similar to the improvement in the quality of life that has been observed among patients who have a response to cisplatin-based chemotherapy.²⁹ Most studies show that there is a deteriora-

tion in the quality of life over time, which is consistent with the results in the standard care group in our study.³⁰⁻³² Despite similar cancer therapies in our two study groups, the patients assigned to early palliative care had an improved quality of life, as compared with those receiving standard care. Rates of depression also differed significantly between the groups, with approximately half as many patients in the palliative care group as in the standard care group reporting clinically significant depressive symptoms on the HADS, and this effect was not due to a between-group difference in the use of antidepressant agents.

To date, evidence supporting a benefit of palliative care is sparse, with most studies having notable methodologic weaknesses, especially with respect to quality-of-life outcomes.⁸ One study with sufficient power to examine quality-of-life outcomes showed that among patients receiving radiation therapy, a multidisciplinary intervention focused on education, behavioral modification, and coping style resulted in improvements in the quality of life.³³ A recent study showed that Project ENABLE (Educate, Nurture, Advise, Before Life Ends), a telephone-based, psychoeducational program for patients with advanced cancer, significantly improved both quality of life and mood.³⁴ However, the percentage of patients who completed the study assessments was somewhat low, and the study did not use a traditional palliative care model.

Our study also showed that early outpatient palliative care for patients with advanced cancer can alter the use of health care services, including care at the end of life. Other studies of outpatient palliative care have failed either to investigate these outcomes or to show an effect on the use of resources.^{5,34,35} In our trial, significantly more patients in the group assigned to early palliative care than in the standard care group had resuscitation preferences documented in the outpatient electronic medical record, an essential step in clarifying and ensuring respect for patients' wishes about their care at the end of life.³⁶ Early introduction of palliative care also led to less aggressive end-of-life care, including reduced chemotherapy and longer hospice care. Given the trends toward aggressive and costly care near the end of life among patients with cancer, timely introduction of palliative care may serve to mitigate unnecessary and burdensome personal and societal costs.^{20,37}

Our study has several advantages over previous studies, in which investigators have often relied on referrals to palliative care instead of using a recruitment approach designed to obtain a representative sample.^{5,35} Because all patients with a new diagnosis of metastatic non–small-cell lung cancer were eligible for enrollment in our study, we extended the generalizability of our findings. Another strength of our trial was the low rate of loss to follow-up and the high percentage of participants who completed the study assessments. In addition, the dropout rate by week 12 was less than 1%, further supporting the feasibility and acceptability of early palliative care. Finally, the trial was adequately powered to detect changes in both quality of life and mood, and we prospectively collected data on end-of-life care.

Several limitations of the study deserve mention. It was performed at a single, tertiary care site with a specialized group of thoracic oncology providers and palliative care clinicians, thereby limiting generalization of the results to other care settings or patients with other types of cancer. In addition, because the sample lacked diversity with respect to race and ethnic group, we were unable to assess the effect of these important factors on study outcomes. Although we used a randomized, controlled design, both the patients and the clinicians were aware of the study assignments. To account for possible influences of care that are not specific to the palliative care provided, follow-up investigations should include a control group that receives a similar amount of attention. In addition, we did not deny palliative care consultations to participants receiving standard care, and a small minority of patients in the standard care group was seen by the palliative care team. The data from these patients were analyzed with the data from their assigned study group (standard care), a factor that may have diluted our findings. Finally, carrying the last observation forward for all missing data in the intention-to-treat analyses is a conservative approach; therefore, the actual treatment effect of early palliative care may be greater than we report.

Early integration of palliative care for patients with metastatic non–small-cell lung cancer is a clinically meaningful and feasible care model that has effects on survival and quality of life that are similar to the effects of first-line chemotherapy in such patients.^{28,38,39} As compared with

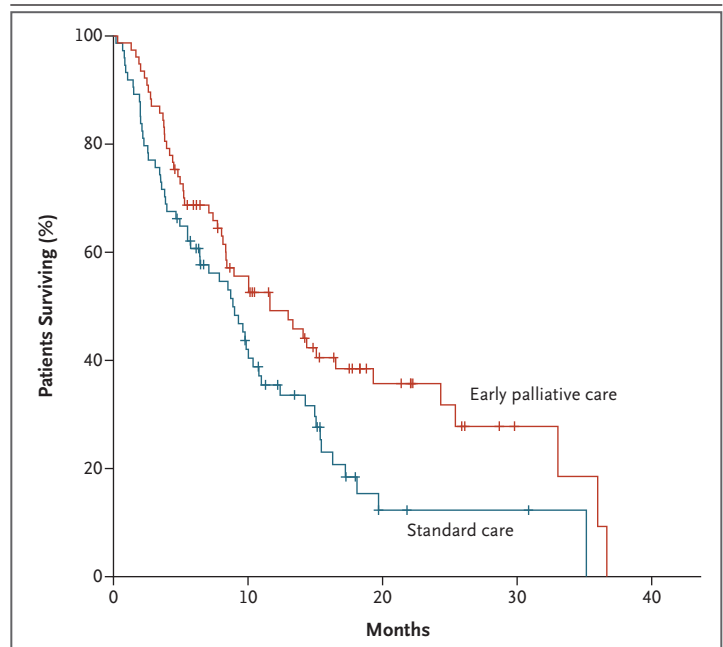


Figure 3. Kaplan–Meier Estimates of Survival According to Study Group.

Survival was calculated from the time of enrollment to the time of death, if it occurred during the study period, or to the time of censoring of data on December 1, 2009. Median estimates of survival were as follows: 9.8 months (95% confidence interval [CI], 7.9 to 11.7) in the entire sample (151 patients), 11.6 months (95% CI, 6.4 to 16.9) in the group assigned to early palliative care (77 patients), and 8.9 months (95% CI, 6.3 to 11.4) in the standard care group (74 patients) ($P=0.02$ with the use of the log-rank test). After adjustment for age, sex, and baseline Eastern Cooperative Oncology Group performance status, the group assignment remained a significant predictor of survival (hazard ratio for death in the standard care group, 1.70; 95% CI, 1.14 to 2.54; $P=0.01$). Tick marks indicate censoring of data.

the study participants who received standard care, those who were assigned to early palliative care had improved mood, more frequent documentation of resuscitation preferences, and less aggressive end-of-life care. Although our findings must be replicated in a variety of care settings and cancer populations, the results nonetheless offer great promise for alleviating distress in patients with metastatic disease and addressing critical concerns regarding the use of health care services at the end of life.

Supported by an American Society of Clinical Oncology Career Development Award and philanthropic gifts from the Joanne Hill Monahan Cancer Fund and Golf Fights Cancer.

Dr. Temel reports receiving payment for developing continuing medical education (CME) programs from InforMEDical; and Dr. Lynch, serving on the board of Infinity Pharmaceuticals, receiving consulting fees from Roche, Boehringer Ingelheim, Merck, AstraZeneca, Bristol-Myers Squibb, and Sanofi-Aventis, royalties from Partners HealthCare, and payment for developing CME programs from InforMEDical. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

- Mongan JJ, Ferris TG, Lee TH. Options for slowing the growth of health care costs. *N Engl J Med* 2008;358:1509-14.
- Weinstein MC, Skinner JA. Comparative effectiveness and health care spending — implications for reform. *N Engl J Med* 2010;362:460-5.
- Ferris FD, Bruera E, Cherny N, et al. Palliative cancer care a decade later: accomplishments, the need, next steps — from the American Society of Clinical Oncology. *J Clin Oncol* 2009;27:3052-8.
- Levy MH, Back A, Benedetti C, et al. NCCN clinical practice guidelines in oncology: palliative care. *J Natl Compr Canc Netw* 2009;7:436-73.
- Follwell M, Burman D, Le LW, et al. Phase II study of an outpatient palliative care intervention in patients with metastatic cancer. *J Clin Oncol* 2009;27:206-13.
- Jordhøy MS, Fayes P, Loge JH, Ahlner-Elmqvist M, Kaasa S. Quality of life in palliative cancer care: results from a cluster randomized trial. *J Clin Oncol* 2001;19:3884-94.
- Morita T, Akechi T, Ikenaga M, et al. Late referrals to specialized palliative care service in Japan. *J Clin Oncol* 2005;23:2637-44.
- Zimmermann C, Riechelmann R, Krzyzanowska M, Rodin G, Tannock I. Effectiveness of specialized palliative care: a systematic review. *JAMA* 2008;299:1698-709.
- Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009;59:225-49.
- Hopwood P, Stephens RJ. Depression in patients with lung cancer: prevalence and risk factors derived from quality-of-life data. *J Clin Oncol* 2000;18:893-903.
- Hopwood P, Stephens RJ. Symptoms at presentation for treatment in patients with lung cancer: implications for the evaluation of palliative treatment. *Br J Cancer* 1995;71:633-6.
- Lutz S, Norrell R, Bertucio C, et al. Symptom frequency and severity in patients with metastatic or locally recurrent lung cancer: a prospective study using the Lung Cancer Symptom Scale in a community hospital. *J Palliat Med* 2001;4:157-65.
- Temel JS, Jackson VA, Billings JA, et al. Phase II study: integrated palliative care in newly diagnosed advanced non-small-cell lung cancer patients. *J Clin Oncol* 2007;25:2377-82.
- Clinical practice guidelines for quality palliative care. 2nd ed. Pittsburgh: National Consensus Project, 2009. (Accessed July 23, 2010, at www.nationalconsensusproject.org.)
- Jackson VA, Jacobsen JC, Greer J, et al. Components of early intervention outpatient palliative care consultation in patients with incurable NSCLC. *J Clin Oncol* 2009;27:Suppl:20635. abstract.
- Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649-55.
- Cella DF, Bonomi AE, Lloyd SR, Tulskey DS, Kaplan E, Bonomi P. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. *Lung Cancer* 1995;12:199-220.
- Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983;67:361-70.
- Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16:606-13.
- Earle CC, Landrum MB, Souza JM, Neville BA, Weeks JC, Ayanian JZ. Aggressiveness of cancer care near the end of life: is it a quality-of-care issue? *J Clin Oncol* 2008;26:3860-6.
- American Society of Clinical Oncology Quality Oncology Practice Initiative. ASCO QOPI summary of measures. Fall 2009. (Accessed July 23, 2010, at <http://qopi.asco.org/Documents/QOPIFall2009MeasuresSummary8-18-09.pdf>.)
- Tang ST, Wu SC, Hung YN, Chen JS, Huang EW, Liu TW. Determinants of aggressive end-of-life care for Taiwanese cancer decedents, 2001 to 2006. *J Clin Oncol* 2009;27:4613-8.
- Temel JS, Greer JA, Admane S, et al. Code status documentation in the outpatient electronic medical records of patients with metastatic cancer. *J Gen Intern Med* 2010;25:150-3.
- Cella D. The Functional Assessment of Cancer Therapy-Lung and Lung Cancer Subscale assess quality of life and meaningful symptom improvement in lung cancer. *Semin Oncol* 2004;31:Suppl 9:11-5.
- Maione P, Perrone F, Gallo C, et al. Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the Multicenter Italian Lung Cancer in the Elderly Study. *J Clin Oncol* 2005;23:6865-72.
- Movsas B, Moughan J, Sarna L, et al. Quality of life supersedes the classic prognosticators for long-term survival in locally advanced non-small-cell lung cancer: an analysis of RTOG 9801. *J Clin Oncol* 2009;27:5816-22.
- Pirl WF, Temel JS, Billings A, et al. Depression after diagnosis of advanced non-small cell lung cancer and survival: a pilot study. *Psychosomatics* 2008;49:218-24.
- Brown J, Thorpe H, Napp V, et al. Assessment of quality of life in the supportive care setting of the Big Lung Trial in non-small-cell lung cancer. *J Clin Oncol* 2005;23:7417-27.
- Cella D, Eton DT, Fairclough DL, et al. What is a clinically meaningful change on the Functional Assessment of Cancer Therapy-Lung (FACT-L) Questionnaire? Results from Eastern Cooperative Oncology Group (ECOG) Study 5592. *J Clin Epidemiol* 2002;55:285-95.
- Bonomi P, Kim K, Fairclough D, et al. Comparison of survival and quality of life in advanced non-small-cell lung cancer patients treated with two dose levels of paclitaxel combined with cisplatin versus etoposide with cisplatin: results of an Eastern Cooperative Oncology Group trial. *J Clin Oncol* 2000;18:623-31.
- Langer CJ, Manola J, Bernardo P, et al. Cisplatin-based therapy for elderly patients with advanced non-small-cell lung cancer: implications of Eastern Cooperative Oncology Group 5592, a randomized trial. *J Natl Cancer Inst* 2002;94:173-81.
- Sandler AB, Nemunaitis J, Denham C, et al. Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2000;18:122-30.
- Rummans TA, Clark MM, Sloan JA, et al. Impacting quality of life for patients with advanced cancer with a structured multidisciplinary intervention: a randomized controlled trial. *J Clin Oncol* 2006;24:635-42.
- Bakitas M, Lyons KD, Hegel MT, et al. Effects of a palliative care intervention on clinical outcomes in patients with advanced cancer: the Project ENABLE II randomized controlled trial. *JAMA* 2009;302:741-9.
- Rabow MW, Dibble SL, Pantilat SZ, McPhee SJ. The comprehensive care team: a controlled trial of outpatient palliative medicine consultation. *Arch Intern Med* 2004;164:83-91.
- Walling A, Lorenz KA, Dy SM, et al. Evidence-based recommendations for information and care planning in cancer care. *J Clin Oncol* 2008;26:3896-902.
- Emanuel EJ, Ash A, Yu W, et al. Managed care, hospice use, site of death, and medical expenditures in the last year of life. *Arch Intern Med* 2002;162:1722-8.
- Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *BMJ* 1995;311:899-909.
- Spiro SG, Rudd RM, Souhami RL, et al. Chemotherapy versus supportive care in advanced non-small cell lung cancer: improved survival without detriment to quality of life. *Thorax* 2004;59:828-36.

Copyright © 2010 Massachusetts Medical Society.