Effects of a Palliative Care Intervention on Clinical Outcomes in Patients With Advanced Cancer
The Project ENABLE II Randomized Controlled Trial

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Fifty percent of persons with cancer are not cured of their disease[1]; however, with improved treatment even patients with advanced disease may live for years. Providing palliative care concurrent with oncology treatment has been proposed to improve quality of life for patients with advanced cancer.[2-8] The National Consensus Project Clinical Practice Guidelines for Quality Palliative Care recommends palliative care referral at the time of a life-threatening diagnosis and other core elements including a multidimensional assessment to identify, prevent, and alleviate suffering; interdisciplinary team evaluation and treatment in selected cases; effective communication skills and assistance with medical decision making; skill in the care of those dying and bereaved; continuity of care; equitable access; and commitment to continued improvement and excellence.[9] However, the evidence supporting many of these recommendations is sparse.[6]

We translated effective strategies from the literature[10,11] and our prior work, including a 3-year palliative care demon-

Context There are few randomized controlled trials on the effectiveness of palliative care interventions to improve the care of patients with advanced cancer.

Objective To determine the effect of a nursing-led intervention on quality of life, symptom intensity, mood, and resource use in patients with advanced cancer.

Design, Setting, and Participants Randomized controlled trial conducted from November 2003 through May 2008 of 322 patients with advanced cancer in a rural, National Cancer Institute–designated comprehensive cancer center in New Hampshire and affiliated outreach clinics and a VA medical center in Vermont.

Interventions A multicomponent, psychoeducational intervention (Project ENABLE [Educate, Nurture, Advise, Before Life Ends]) conducted by advanced practice nurses consisting of 4 weekly educational sessions and monthly follow-up sessions until death or study completion (n=161) vs usual care (n=161).

Main Outcome Measures Quality of life was measured by the Functional Assessment of Chronic Illness Therapy for Palliative Care (score range, 0-184). Symptom intensity was measured by the Edmonton Symptom Assessment Scale (score range, 0-900). Mood was measured by the Center for Epidemiological Studies Depression Scale (range, 0-60). These measures were assessed at baseline, 1 month, and every 3 months until death or study completion. Intensity of service was measured as the number of days in the hospital and in the intensive care unit (ICU) and the number of emergency department visits recorded in the electronic medical record.

Results A total of 322 participants with cancer of the gastrointestinal tract (41%; 67 in the usual care group vs 66 in the intervention group), lung (36%; 58 vs 59), genitourinary tract (12%; 20 vs 19), and breast (10%; 16 vs 17) were randomized. The estimated treatment effects (intervention minus usual care) for all participants were a mean (SE) of 4.6 (2) for quality of life (P=.02), −27.8 (15) for symptom intensity (P=.06), and −1.8 (0.81) for depressed mood (P=.02). The estimated treatment effects in participants who died during the study were a mean (SE) of 8.6 (3.6) for quality of life (P=.02), −24.2 (20.5) for symptom intensity (P=.24), and −2.7 (1.2) for depressed mood (P=.03). Intensity of service did not differ between the 2 groups.

Conclusion Compared with participants receiving usual oncology care, those receiving a nurse-led, palliative care–focused intervention addressing physical, psychosocial, and care coordination provided concurrently with oncology care had higher scores for quality of life and mood, but did not have improvements in symptom intensity scores or reduced days in the hospital or ICU or emergency department visits.

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stration project, Project ENABLE (Educate, Nurture, Advise, Before Life Ends),[12-17] into a multicomponent intervention that was consistent with guideline-essential core elements.[9] Specifically, the intervention included an advanced practice nurse–administered, telephone-based, intensive curriculum, and ongoing assessment and coaching in problem solving, advance care planning, family and health care team communication strategies, symptom management and crisis prevention, and timely referral to palliative care and hospice resources.

We hypothesized that patients exposed to this intervention soon after a new diagnosis of an advanced cancer would become informed, active participants in their care and would experience improved quality of life and mood, symptom relief, and lower resource use over the course of the illness, including at the very end of life compared with patients who received usual care. We also examined caregiver outcomes (eg, caregiver burden, perceptions of end-of-life care, and grief), but a discussion of those results is not included in this article.

METHODS
Study Design
The study was a randomized controlled trial of a palliative care intervention compared with usual care for persons newly diagnosed with advanced cancer. The primary end points were patient-reported quality of life, symptom intensity, and resource use. Mood was a secondary outcome. Enrollment began in November 2003 and ended in May 2007. Data collection of patient-reported outcomes ended on December 31, 2007. However, outcomes that could be monitored via chart review (eg, resource use and vital status) were collected through May 1, 2008. The study protocol and data and safety monitoring board plan were approved by the institutional review boards of the Norris Cotton Cancer Center and Dartmouth College in Lebanon, New Hampshire, and the Veterans Administration (VA) medical center in White River Junction, Vermont. All pa-

tient and caregiver participants signed a document confirming their informed consent.

Patients
Patients identified at the Norris Cotton Cancer Center's tumor boards with a life-limiting cancer (prognosis of approximately 1 year) were eligible if they were within 8 to 12 weeks of a new diagnosis of gastrointestinal tract (unresectable stage III or IV), lung (stage IIIB or IV non–small cell or extensive small cell), genitourinary tract (stage IV), or breast (stage IV and visceral crisis, lung or liver metastasis, estrogen receptor negative [ER–], human epidermal growth factor receptor 2 positive [Her 2 neu+]) cancer. Patients with impaired cognition (<17 on a modified Mini-Mental State Examination),[18] an Axis I psychiatric disorder (schizophrenia, bipolar disorder), or active substance use were excluded. Patients were asked to select a caregiver to participate in the study. Patients who did not select a caregiver were not excluded.

Patients and their caregiver were randomly assigned to the intervention or usual care using a stratified randomization scheme developed for each of the 2 primary sites (Norris Cotton Cancer Center, VA Medical Center). The schemes were stratified by disease and blocked within strata (block lengths of 2 and 4 varied randomly). Research assistants notified the participant of group allocation when the baseline assessment was returned. Referring clinicians were neither informed nor formally blinded to participant assignment.

Intervention
The intervention has been described in detail elsewhere.[19] Briefly, the intervention, based on the chronic care model,[20-23] used a case management, educational approach to encourage patient activation, self-management, and empowerment. We refined and converted the in-person and group strategies used in our prior studies and demonstration project[12-14] to a manualized, telephone-based format to improve access to palliative care in a rural population. One of

2 advanced practice nurses with palliative care specialty training conducted 4 initial structured educational and problem-solving sessions and at least monthly telephone follow-up sessions until the participant died or the study ended. Advanced practice nurses' caseloads were balanced by diagnosis and sex.

The advanced practice nurses began all contacts with an overall assessment by administering the Distress Thermometer, an 11-point rating scale (0-10) of distress recommended by the National Comprehensive Cancer Network guidelines.[24,25] In addition to an overall intensity rating, the Distress Thermometer identified sources of distress in the 5 areas of practical problems (eg, work or school), family problems, emotional problems, spiritual or religious concerns, and physical problems. If distress intensity was rated greater than 3, the advanced practice nurses explored the sources of distress and identified if the participant would like to apply the problem-solving approach to address his or her issues. The nurse then covered the assigned module for that session. The education manual entitled "*Charting Your Course: An Intervention for People and Families Living With Cancer,*" developed during ENABLE I,[13,17,26] contained the 4 modules of problem solving, communication and social support, symptom management, advance care planning and unfinished business, and an appendix listing supportive care resources (available from the authors or at http://www.cancer.dartmouth.edu/palliative/index.shtml).

On average, session 1 (introduction and problem solving) lasted 41 minutes and sessions 2 through 4 each lasted 30 minutes. Following the 4 formal sessions, the advanced practice nurse was readily available by telephone and also contacted the participant (or caregiver) at least monthly (until the participant's death) to follow up on active issues and to assess the need for referral to appropriate care resources (eg, palliative care team, hospice). When concerns were identified, participants were encouraged to contact the oncology or palliative care clinical teams (if they had

received a palliative care team consultation). However, with the participant's permission, the advanced practice nurses would contact the appropriate clinical team about issues requiring attention (eg, unrelieved pain) or referrals to community resources (eg, spiritual counselor).

The clinical teams were responsible for all medical decisions including medication and inpatient care management; however, the advanced practice nurses, in consultation with the team, could facilitate referrals to ancillary resources. Additionally, intervention participants and their caregiver were invited to attend monthly group shared medical appointments (SMAs)[27,28] led by a certified palliative care physician and nurse practitioner. These appointments allowed participants and caregivers to ask questions about medical problems or related issues (eg, symptom management, insurance, social services) and to have more in-depth discussions than is practical during typical clinic visits.[28]

Training of study interventionists in problem solving and group medical appointments was provided by one of the study team psychologists (J.S.). Initial training took approximately 20 hours for the 2 nurse interventionists and 12 hours for the nurse practitioner and physician SMA facilitators. Training methods included didactic presentations, written treatment manuals, and role-playing with feedback (all training materials are available on request from the authors). Thereafter the study team, including the palliative care–certified nurse practitioner and physician, psychologists, and other team members, met biweekly to review the advanced practice nurses' audiotaped educational sessions and to provide feedback on difficult patient management issues.

Usual Care

Participants assigned to usual care were allowed to use all oncology and supportive services without restrictions including referral to the institutions' interdisciplinary palliative care service. The VA Medical Center site had an advanced illness coordinated care program that provided consultation to oncology staff for inpatients with life-limiting illness.

Data Collection and Instruments

Participants completed baseline questionnaires upon enrollment. Follow-up questionnaires were mailed 1 month after baseline and every 3 months until the participant died or study completion (December 31, 2007). Quality of life was measured by the Functional Assessment of Chronic Illness Therapy for Palliative Care.[29,30] This 46-item tool measures physical, emotional, social, and functional well-being in addition to concerns relevant to persons with life-threatening illness (eg, feeling peaceful, reconciling with others). Scores for this tool range from 0 to 184, and higher scores indicate better quality of life (Cronbach α = .80 for our sample). Symptom intensity was measured by a modified Edmonton Symptom Assessment Scale (ESAS).[31,32] The ESAS assessed the 9 symptoms of pain, activity, nausea, depression, anxiety, drowsiness, appetite, sense of well-being, and shortness of breath, using numerical visual analog scales with discrete check boxes (range, 0-10). Scores were multiplied by 10 to allow comparisons with other studies that used a 100-cm line to calculate symptom intensity. The scores in this study range from 0 to 900, which are consistent with other studies, and higher scores indicate greater symptom intensity (Cronbach α = .80 for our sample). Mood was measured by the Center for Epidemiological Studies Depression Scale (CES-D), an established 20-item measure[33,34] with scores from 0 to 60. A score of 16 or higher generally indicates a clinically significant level of depressed mood[33] (Cronbach α = .84 for our sample). Data on resource use (number of days in the hospital, number of days in the intensive care unit [ICU], and number of emergency department visits) and vital status were collected by chart review until death or May 1, 2008. Patients completed a self-report demographic questionnaire including age, sex, ethnicity (Hispanic or Latino), race (white, American Indian/Native Alaskan, Asian, Native Hawaiian/other Pacific Islander, black/African American, or other), religious affiliation, marital status, other members of household, employment status, occupation, and level of education.

Statistical Analysis

The original target sample size of 400 was chosen to provide 80% power to detect treatment effects of at least 0.35 SDs for scores on the Functional Assessment of Chronic Illness Therapy for Palliative Care, ESAS, and CES-D based on a t test comparing the treatment groups with respect to the last observed value with a 2-sided α of .01. However, at the planned study completion date, the final total study enrollment was 322 due to slightly slower accrual than anticipated.

Our primary outcome measures were quality of life (assessed with the Functional Assessment of Chronic Illness Therapy for Palliative Care), symptom intensity (assessed with the ESAS), and resource use. Mood (assessed with the CES-D) was a secondary outcome. For quality of life, symptom intensity, and mood, we conducted 2 sets of longitudinal, intention-to-treat analyses for all participants with baseline and 1 or more follow-up assessments using repeated measures analysis of covariance to examine the effect of the intervention on (1) the total sample in the year after enrollment and (2) the sample of participants who died.

In the first set of analyses, we proceeded forward in time from enrollment. Baseline outcome data were used as adjusting variables. Adjusted means were estimated for the intention-to-treat groups and included all assessment data. For these analyses, we applied a mixed-effects model for repeated measures to the longitudinal data using random-subject effects to account for correlation between repeated outcome measurements on the same individual. Confidence intervals (CIs) and P values were formed for the overall average effects.

The second set of analyses was restricted to the sample of participants who died during the study (as of the final chart

review on May 1, 2008) and had completed both baseline and 1 or more additional assessments. We applied the same intention-to-treat longitudinal model to estimate the mean overall treatment effect for this subsample using the 3 assessments prior to death.

Mean, median, and maximum values were calculated for chart review data on number of days in the hospital, number of days in the ICU, and number of emergency department visits at baseline and the sums of the total days and visits over the length of enrollment. Groups were compared using the Wilcoxon rank sum test.

We examined the baseline covariates that were predictive of missing data and found that both treatment and the baseline outcomes were statistically significant predictors. We then included these as adjusting variables in the analyses to meet the conditions for missing at random.[35] Two-sided $P<.05$ was set as statistically significant. All calculations were performed using SAS software version 9.1 (SAS Institute, Cary, North Carolina).

We did an exploratory, post hoc analysis of survival. We used a log-rank test to compare Kaplan-Meier survival curves for the 2 groups.

RESULTS

Of 1222 patients screened between November 2003 and May 2007, 681 were eligible and were approached and 322 were enrolled (47% participation rate) (**FIGURE 1**). Following consent, participants were randomly assigned to receive usual care (n=161) or the intervention (n=161). Subsequently, 27 individuals assigned to usual care and 16 individuals assigned to the intervention dropped out (Figure 1). A total of 134 participants in the usual care group and 145 participants in the intervention group were analyzed for patient-reported outcomes.

The **TABLE** shows no statistically significant differences at baseline between the intervention and usual care groups for demographic and clinical characteristics, the use of chemotherapy or radiation anticancer treatments, advance directives, palliative care or hospice referral, number of days in the hospital or ICU, or number of emergency department visits. Our sample included slightly more men than is typical of the general population due to the predominant male population at the VA Medical Center recruitment site. During the course of the study, there was no statistically significant difference between the groups relative to the number of participants who received parenteral chemotherapy (72% [116/161] in the usual care group vs 74% [119/161] in the intervention group; Fisher exact test, $P=.80$) or radiation therapy (21% [34/161] in the usual care group vs 22% [36/161] in the intervention group; Fisher exact test $P=.89$).

Of the 681 eligible patients, there were no statistically significant differences between participants (n=322) and nonparticipants (n=359) relative to age, sex, Karnofsky Performance Scale score, referral to hospice, or number of days in the ICU in the prior 3 months.

Quality of Life, Symptom Intensity, and Mood

There were no statistically significant differences at baseline between the groups for the 3 patient-reported outcomes (Table). Longitudinal intention-to-treat analyses for the total sample revealed higher quality of life (mean [SE], 4.6 [2]; $P=.02$) (Functional Assessment of Chronic Illness Therapy for Palliative

Figure 1. Participant Enrollment, Randomization, Treatment, and Data Analysis
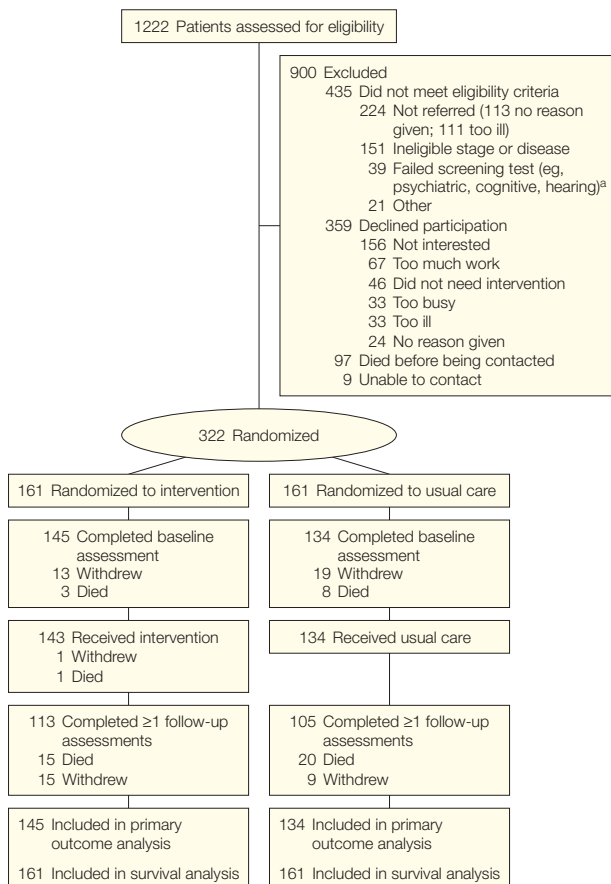
Data on the total number of patients analyzed are missing for the Functional Assessment of Chronic Illness Therapy for Palliative Care (n=130 usual care and n=143 intervention) and for the Center for Epidemiological Studies Depression Scale (n=128 usual care and n=140 intervention) in Figure 2 and Figure 3.
[a]Indicates patients with impaired cognition (<17 on a modified Mini-Mental State Examination), an Axis I psychiatric disorder (schizophrenia, bipolar disorder), or active substance use.

Table. Demographic Characteristics[a]

	Survival Outcomes Sample			Patient Outcomes Sample		
	Intervention (n = 161)	Usual Care (n = 161)	P Value[b]	Intervention (n = 145)	Usual Care (n = 134)	P Value[b]
Age, mean (SD), y	64.7 (10.8)	65.4 (11.6)	.58	65.4 (10.3)	65.2 (11.7)	.89
Male sex	96 (59.6)	91 (56.5)	.65	90 (62.1)	78 (58.2)	.54
Marital status						
Never married	12 (7.4)	15 (9.3)		10 (6.9)	11 (8.2)	
Married or living with partner	116 (72.1)	105 (65.2)	.64	106 (73.1)	90 (67.2)	.75
Divorced or separated	19 (11.8)	23 (14.3)		16 (11.0)	18 (13.4)	
Widowed	14 (8.7)	18 (11.2)		13 (9.0)	15 (11.2)	
Education						
<High school graduate	17 (10.5)	20 (12.4)		17 (11.7)	20 (14.9)	
High school graduate	83 (51.5)	74 (46.0)	.75	83 (57.2)	74 (55.2)	.75
College graduate	43 (26.7)	38 (23.6)		43 (29.7)	38 (28.4)	
Missing	18 (11.3)	29 (18.0)		2 (1.4)	2 (1.5)	
Race[c]						
White	143 (89.0)	132 (82.0)	>.99	143 (98.6)	132 (98.5)	>.99
Other	2 (1.2)	2 (1.2)		1 (0.7)	1 (0.7)	
Missing	16 (9.9)	27 (16.8)		1 (0.7)	1 (0.7)	
Religion						
Protestant	68 (42.2)	60 (37.3)		68 (46.9)	60 (44.8)	
Catholic	44 (27.3)	42 (26.1)	.68	44 (30.3)	42 (31.3)	.68
Jewish	3 (1.9)	1 (0.6)		3 (2.1)	1 (0.7)	
Other	25 (15.5)	29 (18.0)		25 (17.2)	29 (21.6)	
Missing	21 (13.0)	29 (18.0)		5 (3.4)	2 (1.5)	
Work status						
Employed	33 (20.5)	30 (18.6)		29 (20.0)	22 (16.4)	
Retired	80 (49.7)	82 (50.9)	.89	75 (51.7)	70 (52.2)	.64
Not employed	45 (27.9)	48 (30.0)		38 (26.2)	41 (30.6)	
Missing	3 (1.9)	1 (0.6)		3 (2.1)	1 (0.7)	
VA medical center enrollment site	43 (26.7)	41 (25.5)	.90	40 (27.6)	37 (27.6)	>.99
Lives in rural area	86 (53.4)	95 (59.0)	.37	76 (52.4)	81 (60.5)	.19
Caregiver enrolled	116 (72)	104 (64.6)	.19	112 (77.2)	92 (68.7)	.14
Primary disease site						
Gastrointestinal tract	66 (41.0)	67 (41.6)		61 (42.1)	58 (43.3)	
Lung	59 (36.6)	58 (36.0)	>.99	50 (34.5)	43 (32.1)	.98
Genitourinary tract	19 (11.8)	20 (12.4)		19 (13.1)	18 (13.4)	
Breast	17 (10.6)	16 (9.9)		15 (10.3)	15 (11.2)	
Anticancer treatment at enrollment						
Chemotherapy	137 (85.1)	134 (83.2)	.76	107 (73.8)	96 (71.6)	.83
Radiation therapy	20 (12.4)	21 (13.0)	>.99	30 (20.7)	30 (22.4)	.71
Karnofsky Performance Status, mean (SD)[d,e]	77.9 (11.1)	76.6 (13.1)	.35	78.4 (11.1)	77.4 (12.8)	.50
Test score, mean (SD)						
Functional Assessment of Chronic Illness Therapy for Palliative Care (n = 273)				134.0 (22.8)	129.7 (26.2)	.15
Edmonton Symptom Assessment Scale (n = 279)				282.5 (148.8)	286.3 (154.0)	.83
Center for Epidemiological Studies Depression Scale (n = 268)				12.1 (8.5)	13.8 (8.9)	.11
Type of advance directive[e]						
Living will	69 (42.9)	76 (47.2)	.50	63 (43.4)	66 (49.2)	.34
Durable power of attorney for health care	68 (42.2)	78 (48.4)	.31	62 (42.8)	67 (50.0)	.23
Do not resuscitate order	13 (8.1)	10 (6.2)	.67	11 (7.6)	7 (5.2)	.47
Referral to hospice[e]	6 (3.7)	4 (2.5)	.75	4 (2.8)	2 (1.5)	.68
Referral to palliative care[e]	42 (26.1)	51 (31.7)	.32	34 (23.4)	39 (29.1)	.34
Resource use in prior 3 mo, mean (median) [maximum][f]						
Hospital days[e]	2.8 (0) [25]	3.1 (0) [25]	.06	2.6 (0) [25]	2.8 (0) [24]	.60
Intensive care unit days[e]	0.02 (0) [2]	0.04 (0) [2]	.41	0.03 (0) [2]	0.05 (0) [2]	.36
Emergency department visits[e]	0.27 (0) [3]	0.41 (0) [5]	.37	0.28 (0) [3]	0.38 (0) [4]	.62

[a] Values are expressed as number (percentage) unless otherwise indicated. Percentages may not equal 100% due to rounding.
[b] The Fisher exact test was used for categorical variables and the t test was used for continuous variables.
[c] No participants were of Hispanic ethnicity or black race.
[d] For the survival outcomes sample, the total number of patients is 308; for the patient outcomes sample, the total number of patients is 279.
[e] Based on chart review.
[f] Values calculated using the Wilcoxon rank sum test.

Care scores in **FIGURE 2**), a trend toward lower symptom intensity (mean [SE], −27.8 [15]; *P*=.06) (ESAS scores in Figure 2), and lower depressed mood (mean [SE], −1.8 [0.81]; *P*=.02) (CES-D scores in Figure 2) in the intervention group compared with the usual care group.

Longitudinal analyses for the subset of participants who died during the study revealed a similar pattern of effects for higher quality of life (mean [SE], 8.6 [3.6]; *P*=.02) (Functional Assessment of Chronic Illness Therapy for Palliative Care scores in **FIGURE 3**) and no differences in symptom intensity

(mean [SE], −24.2 [20.5]; *P*=.24) (ESAS scores in Figure 3) and lower depressed mood (mean [SE], −2.7 [1.23]; *P*=.03) (CES-D scores in Figure 3) in the intervention group compared with the usual care group.

Resource Use

There were no statistically significant differences between groups in the number of days in the hospital (6.6 vs 6.5, respectively; *P*=.14), number of days in the ICU (0.06 vs 0.06; *P*>.99), or in the number of emergency department visits (0.86 vs 0.63; *P*=.53) (as of the final chart review on May 1, 2008).

Survival

Post hoc, exploratory analyses demonstrated no statistically significant differences in survival between the 2 groups (**FIGURE 4**). Median survival was 14 months (95% CI, 10.6-18.4 months) for the intervention group and 8.5 months (95% CI, 7.0-11.1 months) for the usual care group (log-rank test, *P*=.14). After a mean (SD) follow-up of 14.6 (12.8) months (median, 10.7 months), there were 112 deaths in the intervention group and 119 deaths in the usual care group. Forty-nine participants (30.4%) in the intervention group and 42 participants (26.1%) in

Figure 2. Quality of Life, Symptom Intensity, and Mood Scores for All Patients
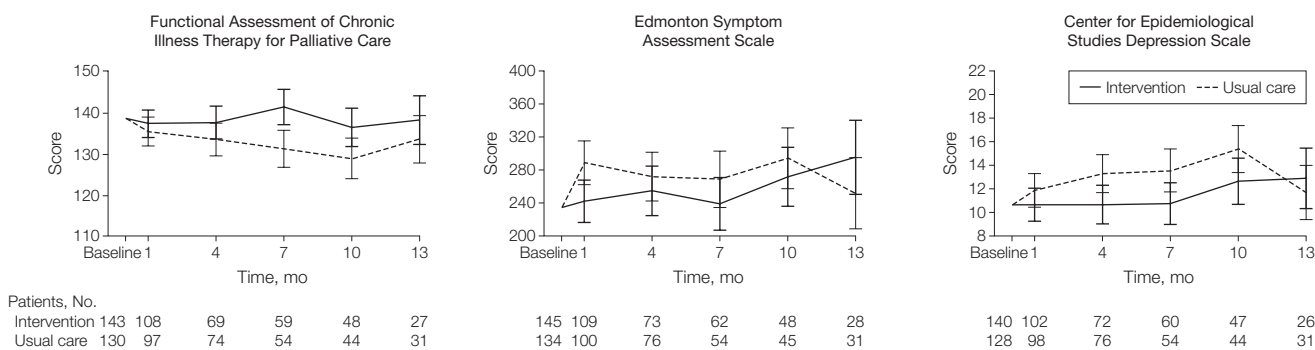
The range for the Functional Assessment of Chronic Illness Therapy for Palliative Care is 0 to 184 (higher scores indicate better quality of life); for the Edmonton Symptom Assessment Scale, 0 to 900 (higher scores indicate greater symptom intensity); for the Center for Epidemiological Studies Depression Scale, 0 to 60 (higher scores indicate more depressive symptoms). Each analysis was adjusted for the respective baseline instrument score. Error bars signify 95% confidence intervals.

Figure 3. Quality of Life, Symptom Intensity, and Mood Scores for Patients Who Died During the Study
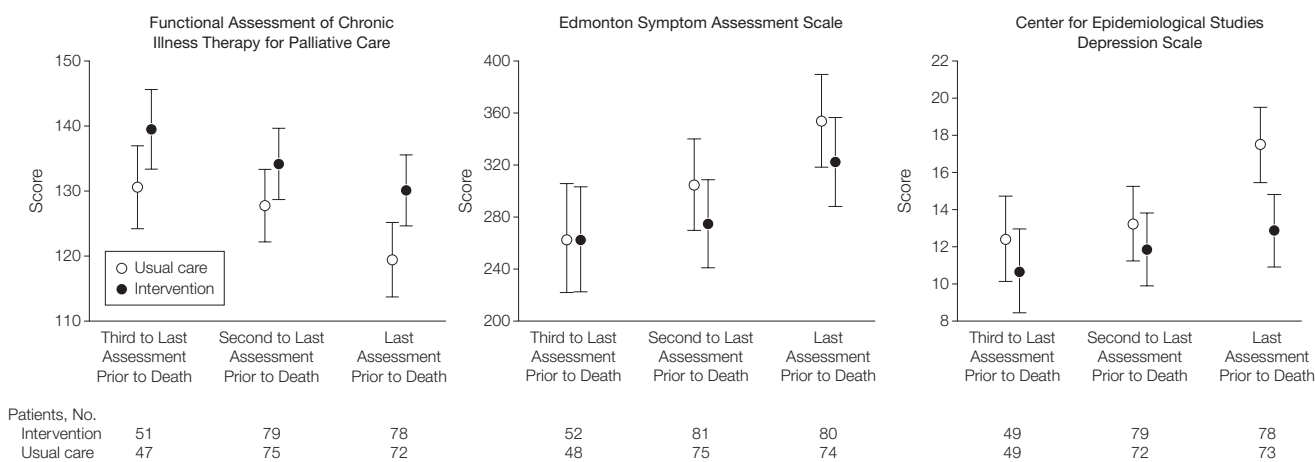
The range for the Functional Assessment of Chronic Illness Therapy for Palliative Care is 0 to 184 (higher scores indicate better quality of life); for the Edmonton Symptom Assessment Scale, 0 to 900 (higher scores indicate greater symptom intensity); for the Center for Epidemiological Studies Depression Scale, 0 to 60 (higher scores indicate more depressive symptoms). Error bars signify 95% confidence intervals.

the usual care group were alive at the final chart review (May 1, 2008) and were censored.

COMMENT

This study shows that integration of a nurse-led palliative care intervention concurrent with anticancer treatments demonstrated higher quality of life (measured by an instrument designed for this specific population),[19,29] lower depressed mood, but limited effect on symptom intensity scores and use of resources in intervention participants relative to those receiving usual cancer care. The intervention had no effect on the number of days in the hospital and ICU, the number of emergency department visits, or anticancer treatment because the proportions of participants in each group receiving these therapies were similar. To our knowledge, this is the first randomized controlled trial designed to test a palliative care intervention concurrent with oncology treatment as has been recommended by international guidelines and consensus recommendations.[2-7,36,37]

A systematic review of specialized palliative care identified 22 trials (16 from the United States) between 1984-2007 with a median sample size of 204, half exclusively with cancer patients.[6] It suggested that evidence for the effectiveness of this care was sparse and limited by methodological shortcomings including control group contamination, recruitment, attrition, and adherence issues. Our trial addressed these issues and contributes to the increasing evidence that palliative care may improve quality of life and mood at the end of life, which are 2 of the main targets of care.[4] In our study, intervention participants' higher quality of life and lower depressed mood may be attributed to improved psychosocial and emotional well-being. Mood is a determinant of the experience of quality of life and suffering despite a mounting burden of physical symptoms.[38] However, while patients in the intervention group had improvement in these outcomes, we conservatively planned our original tar-

get trial enrollment of 400 based on a significance level of .01. Statistical inferences based on this stringent critical value would lead to the conclusion that there were no statistically significant differences between groups in quality of life or mood.

There is no universally accepted definition of the magnitude of difference in quality-of-life scores that is considered clinically meaningful or clinically important.[39-42] Differences between groups of 4% for improvement or 9% for worsening have been cited as clinically meaningful differences using the Functional Assessment of Cancer Therapy tool[39] and we found such between-group differences in our scores. Others have recommended using a distribution-based approach to compare 2 subgroups relative to the SD or SE. Differences between 0.5 and 1 SD or 1 SE are considered statistically significant for most health-related quality-of-life instruments.[40,41] In our study, the quality of life and mood scores demonstrated a greater than 1 SE difference between groups. By these benchmarks, group differences for quality of life and mood achieved clinical significance in addition to statistical significance.

The results did not demonstrate a group difference in symptom intensity as measured by the ESAS. In a systematic review of palliative care effectiveness, which included 14 studies that measured symptom intensity using a variety of scales, only 1 demonstrated improvement of 1 of the targeted symptoms (dyspnea).[6] In that study,[43] the palliative care physician contacted the patients' primary care physician directly with symptom management recommendations. It is possible that an intervention focused primarily on patient empowerment is not robust enough to achieve improved symptom management. Alternatively, the mean ESAS scores (scale range, 0-900) were essentially in the 200s (equivalent to a rating of 2 on a scale of 0 to 10) for both groups. There may be little room for improvement because usual care participants also reported relatively low symp-

Figure 4. Kaplan-Meier Estimates of Survival According to Treatment Group
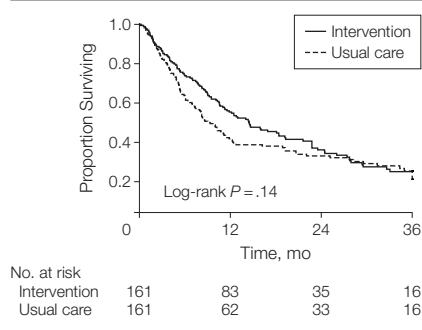
Survival was calculated as the time of enrollment (within 8 weeks of diagnosis with new or recurrent advanced stage disease) to the time of death or study completion (May 1, 2008). Median survival for the intervention group was 14 months (95% CI, 10.6-18.4 months) and 8.5 months (95% CI, 7.0-11.1 months) for the usual care group ($P = .14$).

tom intensity scores compared with patients with advanced cancer in other studies.[19] It may be unrealistic to expect to reduce symptoms further in the setting of progressive disease. Finally, it is possible that symptoms were intermittently improved but the ESAS tool or our data collection schedule may not have been sensitive enough to accurately portray the dynamic, multidimensional symptom experience of this sample.[37] It is not clear which, if any, of these reasons explain why the intervention group had improved quality of life without symptom improvement. However, quality of life and mood are still high-priority patient-centered goals.[44-46]

The intervention was designed to educate and provide ongoing support to patients (from diagnosis to death) with life-limiting cancers and their caregivers about symptom management, advance care planning, treatment decision making, and communication. Beyond education, we hoped to activate patients by coaching them to enhance their coping and problem-solving skills over the illness trajectory.[14,47] The intervention emphasized the importance of patients taking an active role in openly communicating with family and the oncology team regarding their values, priorities, and treatment preferences.

PALLIATIVE CARE INTERVENTION FOR PATIENTS WITH ADVANCED CANCER

There was particular emphasis on communicating during times when anticancer treatments were less likely to halt disease progression or alleviate symptoms.[48] Such communication has recently been demonstrated to be associated with improved quality of life, reduced use of aggressive treatments at the end of life, and increased length of hospice stays.[49] Unlike other studies that were specifically designed to evaluate costs,[50,51] our intervention did not demonstrate reduced use of hospital, ICU, or emergency department resources compared with usual care. However, data collection via chart review may have missed participants' use of resources. Use of databases that may more comprehensively capture costs (eg, Medicare) would address such limitations.[52,53]

Oncology palliative care may lead to positive outcomes by a number of mechanisms. First, interventions may lead to increased social support,[54] patient activation (self-advocacy), or more coordinated and improved medical care. These factors may in turn lead to improved clinical outcomes.[22,23,47] Second, meta-analyses in the United States[55] and Europe[56] of more than 10 000 cancer patients in clinical trials that measured quality of life demonstrated a strong association between higher quality of life and longer survival. Third, palliative and hospice care have been associated with less aggressive cancer care, such as reduced use of chemotherapy in the days before death and reduced inappropriate use of hospital and ICU resources in terminal patients—factors that may influence patients' quality of life.[57] Finally, Nelson et al[58] proposed a biobehavioral model whereby interventions that enhance quality of life may positively influence the psychoneuroimmunologic axis and improve physiological clinical outcomes. Identifying mechanisms of intervention effect on quality of life is an important future area of research.

A number of limitations are worthy of note. First, consistent with the paucity of racial and ethnic diversity in this rural New England region from which our sample was drawn, we had limited ethnic and racial representation and therefore recognize the need to replicate this study with more diverse populations. Second, our intervention was primarily conducted by telephone, a strategy that has shown promise in the delivery of psychotherapy[59] and in encouraging screening behaviors.[60] It is possible that a more robust effect, particularly in reducing symptom intensity, may have been seen with in-person interactions (such as those seen in another successful outpatient palliative care intervention study[61]) rather than our telephone-based approach. However, in-person consultation was often not feasible for our debilitated, rural population, many of whom live more than an hour's drive from the cancer center. Further research is needed to explore optimal care delivery systems in this population.

Institute of Medicine reports,[2,3] the National Consensus Project for Quality Palliative Care,[9] other consensus panels,[62,63] and oncology professional societies[64] agree that comprehensive cancer care must incorporate more than state-of-the-art disease-modifying treatment. Comprehensive, high-quality cancer care includes interdisciplinary attention to improving physical, psychological, social, spiritual, and existential concerns for the patient and his or her family. While our study did not show that early intervention for patients with advanced cancer by a nurse-led program improved symptoms or reduced use of some resources, the study did show that it provides some patients with advanced cancer a higher quality of life and mood.

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