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Clinical Trial Participation as Part of End-of-Life Cancer Care: Associations With Medical Care and Quality of Life Near Death

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Abstract

Context—Clinical trials are a common therapeutic option for patients with advanced incurable cancer.

Objectives—To examine the associations between trial participation and end-oflife (EOL) outcomes, including aggressive care and quality of life (QOL).

Methods—Coping with Cancer, a multicenter prospective cohort study of patients with metastatic cancer, progressed after at least first-line chemotherapy. Baseline chart review documented clinical trial participation. Baseline interviews assessed psychosocial characteristics and EOL preferences. Caregiver interview and chart review assessed medical care and QOL near death. The primary outcome was aggressive EOL care (ventilation, resuscitation, or Intensive Care Unit admission in last week of life). Propensity-score weighting balanced patient characteristics that differed by trial participation, including care preferences and EOL discussion. Propensity-score weighted regression models estimated the effect of trial participation on outcomes.

Results—Of 352 patients followed to death, 37 were enrolled in a clinical trial at baseline. In propensity-score weighted analyses, trial participation was significantly associated with aggressive EOL care (21.6% vs. 12.0%; adjusted odds ratio [AOR], 2.04; 95% confidence interval [CI], 1.00, 4.15), late hospice enrollment (51.4% vs. 42.2%; AOR, 1.96; 95% CI, 1.10, 3.50), hospital death (48.6% vs. 25.7%; AOR, 2.74; 95% CI, 1.37, 5.47), ICU death (16.2% vs. 6.3%; AOR, 3.53; 95% CI, 1.29, 9.65), and inferior QOL near death (least squares mean 5.93 vs. 7.69, $P < 0.001$).

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Controlling for EOL care, trial enrollment was no longer associated with QOL near death (P = 0.342).

Conclusion—Clinical trial participation is associated with aggressive EOL care. Aggressive EOL care appears to explain the association between trial participation and QOL near death.

Keywords

palliative care; end-of-life care; clinical trials; cancer

Introduction

For patients with advanced refractory cancer, experimental therapy, particularly on an early phase clinical trial, is a common therapeutic option.[1] Clinical trials are essential to the process of improving available cancer therapy. Participation, therefore, is strongly encouraged by organizations such as the National Comprehensive Cancer Network, whose guidelines[2] state: “the best management of any cancer patient is in a clinical trial.” This position statement underscores the dual research and therapeutic aims of clinical trials. Although the principal purpose of clinical trials is to generate knowledge in order to improve future therapy,[3] many patients incorrectly believe that the primary purpose of clinical trials is to directly benefit participants.[4] This “therapeutic misconception” threatens the validity of informed consent for cancer clinical trials, and has raised substantial controversy about the place of experimental therapy within the care of patients with advanced cancer.[5–8]

Early phase, and specifically phase I trials, have prompted the most debate among ethicists and oncology clinicians.[5,8–11] Classic phase I trials result in very low response rates (in the range of 5–10%),[12,13] and are designed with nontherapeutic primary aims of determining toxicity and the optimal dose for subsequent testing.[13] Unfortunately, most participants misunderstand the purpose of early phase trials,[14] and enroll anticipating a substantial likelihood of personal benefit, and even cure.[1,8,15–17] Despite the fact that phase I trials infrequently provide direct benefit to participants and are primarily designed to contribute to scientific knowledge, most patients with advanced cancer enroll in early phase trials primarily in hopes of personal benefit, rather than for altruistic reasons.[14,18] Nevertheless, several highly successful early phase trials involving targeted cancer therapies demonstrated that drugs in early development can occasionally provide significant benefit to patient-subjects,[19–21] and support their place within the care of appropriately informed patients.[9]

For patients with very limited life expectancy, the decision to pursue investigational therapy can be particularly difficult.[11] Although many patients are highly motivated to continue disease-directed treatment,[22] national guidelines[23] support balancing this desire with other goals of quality end-of-life (EOL) care including symptom control, avoiding futile interventions, and supporting patients’ ability to come to terms with and prepare for death.[24–26] Beyond weighing the odds of disease response and toxicity, the risks and benefits of trial participation upon these EOL goals merit consideration.[11] For example, pursuing investigational therapy might help patients feel that they have fought cancer to the best of their ability, and thereby find greater acceptance and peace at EOL. Conversely, trial

participation might distract some patients from coming to terms with death and making EOL plans.

Despite an extensive literature devoted to the ethics of early phase oncology trials,[1,9,16,22] to our knowledge the impact of trial participation on cancer patients' medical care and quality of life (QOL) near death has not been investigated. We sought to examine the relationships between cancer clinical trial participation and goals of quality EOL care including patients' acceptance of terminal illness, advance care planning, use of aggressive medical interventions, and QOL near death.

Methods

Study Sample

Coping with Cancer was a multi-institutional, prospective cohort study of patients with advanced cancer designed to examine how psychosocial factors influence patient's outcomes at EOL. Subjects were recruited between September 2002 and February 2008 from seven outpatient sites: Yale Cancer Center (New Haven), Veterans Affairs Connecticut Healthcare System Comprehensive Cancer Clinics, Memorial Sloan-Kettering Cancer Center (New York), Simmons Comprehensive Cancer Care Center and Parkland Hospital Palliative Care Service (Dallas), Massachusetts General Hospital and Dana-Farber Cancer Institute (Boston), and New Hampshire Oncology-Hematology. Patient eligibility criteria were: (1) diagnosis of an advanced cancer with metastases, (2) disease progression following first-line chemotherapy, (3) age at least 20 years, (4) presence of an informal caregiver, and (5) adequate stamina to complete the interview. Patient-caregiver dyads in which either patient or caregiver refused to participate, met criteria for dementia or delirium,[27] or did not speak English or Spanish were excluded. Both patients and caregivers provided written informed consent in accordance with protocols approved by the institutional review boards of each participating site.

Of 993 eligible patients, 718 (72.3%) enrolled. Sociodemographic characteristics of participants and nonparticipants did not differ, except that participants were more likely to be Hispanic (12.1% vs. 5.8%; $P = 0.005$). For the present analysis, we used the 358 patients with non-missing data for clinical trial enrollment at baseline and who died by August 2008. The deceased cohort with non-missing clinical trial enrollment data did not differ significantly ($P<0.05$) by cancer type or psychological distress, but as expected was more debilitated (e.g., worse performance status and higher symptom burden) and more likely to have characteristics associated with lower socioeconomic status (e.g., less educated, ethnic minority).

Protocol

Patients and caregivers participated in separate baseline interviews ($25 compensation) in English or Spanish, conducted by trained research assistants. At baseline, research staff reviewed the medical record to confirm information about the patient's clinical condition and treatment. Within two to three weeks of each patient's death, the formal or informal caregiver most involved during the patient's death was contacted to provide information

regarding the patient's care and QOL in the last week of life. Further information on health care received near death was obtained from the medical chart.

Baseline Measures

Clinical Characteristics—Chart review determined clinical characteristics, including cancer diagnosis and treatment, and whether the patient was currently participating in a clinical drug trial (yes/no). Study assistants indicated the phase of trial when apparent in the chart. Charlson Comorbidity Index (CCI)[28] assessed comorbid medical conditions.[28] Treating physicians indicated Karnofsky[29] and Eastern Cooperative Oncology Group (ECOG) performance status.

Demographic and Psychosocial Characteristics—At baseline, patients reported age, gender, marital status, family income (≥ $31,000 vs. <$31,000), years of education, and religious affiliation. Patients indicated their race/ethnicity, because of its known importance to EOL care utilization.[30] The McGill Quality of Life Questionnaire (MQOL),[31] including physical, psychological, and support subscales, assessed QOL. The Brief COPE Survey assessed active, emotion-focused, and maladaptive methods of coping with cancer-related stress.[32] Pargament's brief RCOPE assessed positive religious coping (e.g., seeking spiritual support) and negative religious coping (e.g., questioning God's love).[33]

Illness Understanding, Treatment Preferences, and Advance Care Planning—At baseline, patients were asked to describe their current health status; those responding "seriously and terminally ill" were considered to acknowledge their terminal illness. Patients indicated if they had previously discussed their wishes regarding EOL care with their physicians.[25] An item from the SUPPORT study[34] assessed if patients preferred care focused on life-extension, or care focused on relieving pain and discomfort. Fried's Willingness to Undergo Life-Sustaining Technologies measured patients' willingness to be admitted to an Intensive Care Unit (ICU), be on a ventilator, have a feeding tube, or receive chemotherapy near death.[35] Patients indicated whether they had had completed a do-not-resuscitate (DNR) order, a living will, or health care proxy.

Outcomes

EOL Care Outcomes—The primary outcome was receipt of aggressive EOL care, defined as mechanical ventilation, resuscitation, or ICU admission in the last week of life. Other outcomes included hospice services, location of death (hospital, ICU, or home), and number of aggressive procedures received in the final week (because of its correlation with poor quality of death).[25]

Patient QOL at EOL—Caregivers were asked in the post-mortem interview: "In your opinion, how would you rate the overall quality of the patient's last week of life?" Response options ranged from 0 ("worst possible") to 10 ("best possible") on a Likert scale. Physical and psychological distress were assessed with identical response options. This measure has been correlated with the validated Quality of Dying and Death scale[36] and is predictive of caregivers' bereavement adjustment.[25] Further validating caregivers' evaluation of patients'

QOL, caregivers completed the MQOL for the patient at baseline; this score was significantly ($P<0.001$) associated with the patient's self-reported MQOL score.[37]

Statistical Methodology

Significant associations between trial enrollment and baseline characteristics were tested using *t*-tests and Kruskal-Wallis tests for continuous variables, and Chi-square and Fisher's exact tests for dichotomous variables.

The relationships between trial enrollment and terminal illness acknowledgment, desire for prognostic information, EOL care preferences, EOL discussion, and advance care planning were examined using multivariable logistic regression models. Sociodemographic and clinical characteristics (age, gender, income, marital status, insurance, education, race/ethnicity, religion, recruitment site, cancer type, performance status, CCI, baseline MQOL and subscales, coping, and religious coping) were entered into each model when associated with the predictor (trial enrollment) and outcome with $P<0.10$, and retained in the model if associated with $P<0.05$.

Propensity-score multiple imputation[38] was used to impute missing data for baseline covariates based upon the non-missing baseline covariates and outcome measures. Rates of missing baseline data were low (under 2% for most demographic and clinical characteristics, and under 12% for most psychosocial variables) with the exception of income (41.6% missing). Five complete datasets were imputed based upon the missing at random assumption using SOLAS for Missing Data Analysis Version 4.0 (Statistical Solutions, Saugus, MA).

The propensity-score weighting technique was used to balance characteristics that differed significantly (P-value <0.10) according to trial participation. These included: the patient's sociodemographic and clinical characteristics, baseline QOL, coping, EOL discussion, EOL care preferences and advance care planning. In each multiply imputed dataset, logistic regression models estimated the odds of clinical trial enrollment as a function of these characteristics. The propensity scores from the five multiply imputed datasets were averaged to obtain the final propensity score for adjusted analyses. The averaged propensity score was normalized by dividing the mean in each treatment group, and then used to derive individual weights equal to the probability of belonging to the opposite group, making the weighted distribution of characteristics among participants in both groups balanced and adjusting for potential confounding effects from the characteristics associated with clinical trial enrollment.[39]

Propensity-score weighted logistic regression was used to estimate the effect of clinical trial enrollment on binary outcomes (e.g., EOL care) and propensity-score weighted linear regression models estimated their effect on continuous measures (e.g., QOL in the last week of life). Regression models also were adjusted for age, gender, race, education, biliary cancer, and the propensity score.

Statistical analyses were performed with SAS version 9.2 (SAS Institute Inc., Cary, NC). Two-sided P-values were used.

Results

Patient Characteristics

The cohort comprised 358 terminally ill cancer patients who died a median of 3.9 months after enrollment (mean±SD = 6.3±6.5 months). The sociodemographic, clinical, and psychosocial characteristics of the cohort at baseline are listed in Table 1. At baseline, 37 (10.5%) patients were enrolled in a clinical trial. Of these patients, 10 were enrolled in phase I trials, nine were in phase II trials, five were in phase III trials, and the phase of trial was unknown for 13 patients. At baseline, 196 (55.7%) patients were receiving chemotherapy and 24 (6.8%) patients were receiving radiation or chemo-radiation therapy.

Clinical trial participants were less likely to be an ethnic minority (P=0.012), more likely to have health insurance (P<0.001), and more likely to be recruited from Yale than patients not in a clinical trial (P<0.001). Trial participants had better Karnofsky (P=0.009) and ECOG (P=0.017) performance status scores, and fewer comorbidities (P =0.007). Trial participation was not associated with MQOL or coping styles.

Prognostic Acceptance, Treatment Preferences, and Advance Care Planning

In multivariable logistic regression models (Table 2), clinical trial participants were significantly less likely to want prognostic information (adjusted odds ratio [AOR], 0.34; 95% confidence interval [CI], 0.16, 0.71), and were less likely to have had an EOL discussion (AOR, 0.30; 95% CI, 0.11, 0.78). Significant bivariate associations found between trial participation and lower rates of DNR order completion, and preference for life-extending care became non-significant after adjusting for confounders.

Propensity Score Adjustment

After propensity-score weighting (Table 3), participants no longer differed on the factors that distinguished clinical trial participants from patients not in a trial, specifically: insurance status, race/ethnicity, religion, recruitment site, cancer type, performance status, comorbidity, symptoms, desire for prognostic information, EOL discussion, preference for life-extending care or chemotherapy, or DNR order.

Patients' Medical Care and QOL at the EOL

Table 4 shows EOL care and QOL at EOL according to enrollment in a clinical trial. In adjusted analyses, clinical trial enrollment was significantly associated with increased receipt of aggressive EOL care (21.6% vs. 12.1%; AOR, 2.04; 95% CI, 1.00, 4.15), ICU admission (21.6% vs. 11.1%; AOR, 2.26; 95% CI, 1.09, 4.67), mechanical ventilation (21.6% vs. 5.7%; AOR, 8.22; 95% CI, 3.02, 22.40), and late hospice enrollment (51.3% vs. 42.2%; AOR, 1.96; 95% CI, 1.10, 3.50). Clinical trial participation also was significantly associated with increased number of aggressive procedures near death, and increased risk of death in the hospital (AOR, 2.12; 95% CI, 1.24, 3.60) or the ICU (AOR, 3.53; 95% CI, 1.29, 9.65).

In adjusted analyses, trial participants had significantly worse global QOL (least squares mean, 5.93 vs. 7.69, P<0.001), physical distress (P<0.001), and psychological distress

($P<0.001$) in their final week of life as compared with patients who were not enrolled in a trial. To test whether aggressive EOL care was responsible for (i.e., mediated) the observed relationship between trial enrollment and global QOL at EOL, the model was further adjusted for receipt of hospice and aggressive EOL care. After these adjustments, trial participation was no longer related to QOL at EOL (5.22 vs. 5.67, $P = 0.342$).

Discussion

In this prospective study of patients with progressive incurable cancer, we found clinical trial participation to be associated with increased risk for aggressive medical care near death, despite rigorous adjustment for demographic, clinical, and psychosocial factors. This finding is troublesome given the poor outcomes of patients with advanced cancer receiving intensive medical care near death,[40] and the harm that intensive EOL care may inflict on patients' QOL[37] and caregivers' bereavement.[25] Because causation cannot be conclusively determined from observational studies, it is uncertain whether trial participation is a marker of, or responsible for, increased risk of aggressive EOL care. Potential explanations include factors related to patients, providers, or the environment of care in clinical trials.

The accuracy of patients' prognostic understanding,[34] patient-physician discussions about EOL care preferences,[25,41] and patients' preference for comfort-oriented care[34] have been previously demonstrated to protect against the receipt of aggressive and futile medical care near death. At baseline, trial participants were notably disinclined to receive prognostic information, were unlikely to have had an EOL discussion, and consistent with prior research,[1] were more likely to value care focused on life-extension rather than comfort. Because propensity-score weighting neutralized these observed differences between patients enrolled and those not enrolled in a trial, higher rates of intensive EOL care observed among trial participants cannot be attributed to baseline differences in EOL care preferences or EOL/prognostic conversations. We were unable to examine or control for changes in care preferences or EOL/prognostic conversations that may have occurred subsequent to the baseline assessment. Future research, including repeated, longitudinal assessments of these factors, will be necessary to more fully characterize the relationships between trial enrollment, patients' EOL care preferences, prognostic/EOL discussions, and their influence on patients' subsequent medical care and QOL at EOL.

Physician-related factors also might explain our findings. Trial enrollment could be an indicator of physicians' more aggressive pattern of practice, or a reluctance to discuss prognosis and EOL planning. Research has suggested that oncologists and patients frequently avoid prognostic discussions by focusing on concrete treatment details, even when confronted by disease progression.[42] This avoidance may stem from physicians' discomfort discussing EOL issues, or physicians may selectively avoid these conversations with patients perceived to be disinterested in or unprepared to confront prognosis and EOL planning. In these cases, discussing an experimental protocol might be easier than engaging in the difficult conversations that are unavoidable when no disease modifying therapy is available. For example: one study of audio-recorded phase I trial informed consent conversations found that prognosis was discussed in only 20% of visits.[43] Investigational therapy deserves consideration for many patients; however, this decision should be

predicated upon candid discussions about prognosis and EOL preferences.[11,23,43] Interventions directed at improving EOL communication or the informed consent process[44] might support cancer patients' prognostic understanding and promote informed EOL decision making.

Other factors related to patients' experience of care in a trial might contribute to aggressive EOL care. First, clinical trials are an important source of hope for cancer patients, many of whom have been shown to have overly optimistic expectations of benefit.[8,14–16] Although therapeutic optimism may protect participants from sadness and depressive symptoms,[45] such unrealistic hopes might conversely interfere with the normal grief process required to accept and prepare for death.[46] Second, trial participation perpetuates close interaction between patients and the medical system through an intensive schedule of clinic visits, treatments, and testing. As a patient's health deteriorates, involved providers may feel compelled to act upon observed medical problems, even if patients are nearing death. These proposed mechanisms are somewhat speculative and require further study.

It should be noted that intensive EOL care may be consistent with the wishes of some cancer patients and, therefore, is not always an undesirable outcome. We have previously demonstrated that patients who receive the type of EOL care they prefer, even if it is more aggressive, have better QOL near death as compared with patients who receive care that is inconsistent with their stated preferences.[47] In this present analysis, trial participants were observed to prefer more aggressive EOL care (Table 2) as compared with patients not enrolled in a trial. Propensity weighting effectively neutralized those differences (Table 3). Thus, in the analysis using the propensity-score weighted sample (Table 4), the increased rate of aggressive EOL care observed among trial participants is not explained by a preference for intensive EOL care reported at baseline. Future research including longitudinal assessments of patient preferences will be necessary to understand better how trial enrollment influences patients' care preferences over time, and how these factors may in turn influence receipt of aggressive EOL care, as well as receipt of EOL care consistent with patients' ultimate wishes.

Consistent with prior research,[25] we found that receipt of intensive EOL care explained the poor quality of death associated with trial enrollment. Although many trial participants are willing to endure treatment-related suffering in hopes of prolonged survival,[22] research also suggests that they value QOL similarly to length of life.[1,15,48] Lastly, early phase trial participants are known to experience a high burden of symptoms,[49] and are interested in advance care planning.[50] Integrated palliative care services, which improve cancer patients' QOL and prognostic understanding without compromising survival,[24] might be an ideal intervention to support trial participants' QOL and EOL planning. Integrated home-based supportive care services,[51] or expanding hospice benefits to patients in early phase trials[52] are other potential interventions that might improve the QOL of patients with advanced cancer enrolled in trials.

This study has many strengths, including its novelty, extensive baseline assessments, and prospective evaluation of medical care and QOL at EOL. Nevertheless, our results must be interpreted in the context of an observational study. Although propensity-weighted models

adjusted for a wide array of patient characteristics, unmeasured confounds are possible. Additionally, trial participation was only assessed at baseline, and phase of trial information was incomplete. Clinical trial enrollment occurring after the initial assessment would not be captured by our study design; however, this would be expected to bias our results toward the null hypothesis, making our results conservative. Furthermore, only 37 subjects were enrolled in a clinical trial at baseline. Confirmation of our findings within a larger patient sample, or one enriched for trial participants, would enhance the generalizability of our findings. Despite these limitations, the influence of clinical trial participation on cancer patients' QOL and medical care near death has been minimally studied. Our results are important but should be considered hypothesis generating; future studies should be designed specifically to assess relationships between cancer clinical trial participation and a broader dimension of relevant EOL outcomes including patient QOL while in a trial, satisfaction with care, and health care utilization near death.

In summary, in this prospective study of patients with advanced incurable cancer, we found clinical trial participation to be associated with increased risk for aggressive EOL care and poor QOL near death. In view of the necessity of clinical trials to improve available cancer treatment and the importance supporting patients' participation in this process, efforts are needed to promote the successful incorporation of investigational therapy into the continuum of quality EOL care.

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Table 1

Baseline Sociodemographic and Clinical Characteristics

		Enrollment in a Clinical Trial at Baseline		
Patient Characteristic	**Total *N* = 358**	**In Trial *n*=37 *n* (%)**	**Not in Trial *n*=321 *n* (%)**	***P*-value**
Demographic Characteristics				
Age, yrs, mean±SD	356	56.3±11.8	58.9±12.7	0.241
Male gender	356	16 (43.2%)	178 (55.8%)	0.165
Income >$31,000	209	12 (63.2%)	101 (53.2%)	0.474
Married	353	26 (70.3%)	191 (60.4%)	0.287
Health Insurance	351	34 (91.9%)	186 (59.2%)	<**0.001**
Education, yrs, mean±SD	356	13.4±3.5	12.4±4.1	0.179
Race/Ethnicity	356			**0.012**
White		30 (81.1%)	205 (64.3%)	**0.044**
Black		3 (8.1%)	58 (18.2%)	0.166
Hispanic		2 (5.4%)	51 (16.0%)	0.139
Asian		2 (5.4%)	2 (0.6%)	0.055
Religion	356			
Catholic		17 (45.9%)	115 (36.1%)	0.281
Protestant		3 (8.1%)	58 (18.2%)	0.166
Baptist		3 (8.1%)	50 (15.7%)	0.328
Pentecostal		1 (2.7%)	8 (2.5%)	1.000
Jewish		5 (13.5%)	12 (3.8%)	**0.023**
Muslim		1 (2.7%)	3 (0.9%)	0.357
None		1 (2.7%)	15 (4.7%)	1.000
Recruitment Site	357			
Yale Cancer Center		21 (56.8%)	47 (14.7%)	<**0.001**
Veterans Affairs CCC		0 (0.0%)	12 (3.8%)	0.622
Simmons Cancer Center		3 (8.1%)	31 (9.7%)	1.000
Parkland Hospital		5 (13.5%)	136 (42.5%)	<**0.001**
Dana Farber and Massachusetts General Hospital		1 (2.7%)	7 (2.2%)	0.587
New Hampshire Oncology Hematology		3 (8.1%)	62 (19.4%)	0.115
Clinical Characteristics				
Cancer Type	358			
Lung		3 (8.1%)	73 (22.7%)	0.053
Pancreatic		9 (24.3%)	24 (7.5%)	**0.003**
Colon		6 (16.2%)	39 (12.1%)	0.439
Gastric		1 (2.7%)	13 (4.0%)	1.000
Esophageal		3 (8.1%)	9 (2.8%)	0.116
Biliary		0 (0.0%)	7 (2.2%)	1.000
Brain		2 (5.4%)	6 (1.9%)	0.196

		Enrollment in a Clinical Trial at Baseline		
Patient Characteristic	**Total *N* = 358**	**In Trial *n*=37 *n* (%)**	**Not in Trial *n*=321 *n* (%)**	***P*-value**
Performance status, mean±SD				
Karnofsky Score[a]	349	71.1±17.5	63.5÷16.3	**0.009**
ECOG Score[b]	351	1.4±0.9	1.8±0.9	**0.017**
Charlson Comorbidity Index[c]	357	7.2±2.4	8.6±2.7	**0.007**
McGill QOL[d], mean±SD	355			
Sum Score		7.1±1.1	6.8±1.6	0.145
Physical function		6.0±2.0	5.6±2.7	0.267
Symptoms		6.1±1.6	5.3±2.2	**0.004**
Psychological		7.6±2.2	7.2±2.5	0.343
Support		8.4±1.4	8.7±1.7	0.331
Psychosocial Characteristics				
Brief COPE[e], mean±SD				
Emotional support-based coping	326	2.5±0.6	2.5±0.7	0.615
Active coping	325	2.0±0.7	1.8±0.9	0.185
Behavioral disengagement	324	0.2±0.5	0.3±0.6	0.424
RCOPE[f], mean ± SD				
Positive RCOPE	319	10.3±6.7	11.2±6.2	0.453
Negative RCOPE	317	1.6±2.9	2.0±3.6	0.346
Attitudes toward EOL care				
Terminal illness acknowledgment	322	9 (27.3%)	116 (40.1%)	0.188
Desires prognostic information	326	15 (50.0%)	220 (74.8%)	**0.006**
EOL discussion	357	6 (16.2%)	145 (45.3%)	<**0.001**
EOL care preferences & advance care planning				
Values life-extension over comfort	290	14 (48.3%)	69 (26.4%)	**0.018**
Against ICU death	327	12 (36.4%)	109 (37.1%)	1.000
Prefer ventilator	323	9 (28.1%)	75 (25.8%)	0.832
Prefer feeding tube	319	11 (34.4%)	114 (39.7%)	0.703
Prefer chemotherapy	320	29 (93.5%)	219 (75.8%)	**0.023**
DNR order	323	8 (25.0%)	130 (44.7%)	**0.038**
Living will or health care proxy	321	18 (54.5%)	163 (56.6%)	0.854

[a] Karnofsky score: 0 is dead and 100 is perfect health.

[b] ECOG: 0 is no limitations and 4 is completely bed-bound.

[c] Age-adjusted measure of comorbid illness, where higher numbers signify a greater burden.

[d] The McGill QOL subscales range from 0–10, where 0 is undesirable and 10 is desirable.

[e] Carver's Brief Cope measures use of specific types of coping, with scores ranging from 0 (none) to 6 (most).

[f] Measures use of positive and negative religious coping, with scores ranging from 0 (none) to 21 (most).

Table 2

Adjusted Associations[a] of Clinical Trial Enrollment With Terminal Illness Acknowledgment, EOL Care Preferences, and Advance Care Planning; *N* = 358

	Total	**Enrollment in Trial**		**Unadjusted Analyses**		**Adjusted Analyses**	
	***n/N* (%)**	**Yes; *n*=37**	**No; *n*=321**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Terminal illness acknowledgment	125/322 (38.8)	9 (27.3)	116 (40.1)	0.56 (0.25,1.25)	0.155	0.72 (0.30, 1.71)	0.458
Desires prognostic information	236/326 (72.4)	16 (50.0)	220 (74.8)	0.34 (0.16, 0.71)	**0.004**	0.37 (0.18, 0.79)	**0.01**
Values life-extension over comfort	83/290 (28.6)	14 (48.3)	69 (26.4)	2.60 (1.19, 5.66)	**0.016**	2.02 (0.86, 4.75)	0.108
EOL discussion	151/357 (42.3)	6 (16.2)	145 (45.3)	0.23 (0.09, 0.58)	**0.002**	0.30 (0.11, 0.78)	**0.014**
DNR order	138/323 (42.7)	8 (25.0)	130 (44.7)	0.41 (0.18, 0.95)	**0.037**	0.51 (0.20, 1.26)	0.142
Living will or health care proxy	181/321 (56.4)	18 (54.5)	163 (56.6)	0.92 (0.45, 1.90)	0.821	0.77 (0.35, 1.73)	0.532

[a]Analyses were adjusted for sociodemographic and clinical confounders. Covariates of age, gender, income, marital status, insurance, education, race/ethnicity, religion, recruitment site, cancer type, performance status, Charlson Comorbidity Index, McGill QOL and subscales, coping, and religious coping were entered into models when related to clinical trial enrollment and the outcome of interest with $P<0.10$, and were retained in the model when remaining significant with $P<0.05$.

Table 3

Adjusted Association of Baseline Sociodemographic and Clinical Characteristics With Clinical Trial Enrollment After Propensity Weighting; $N = 352$[a]

	Enrollment in a Clinical Trial at Baseline		
Patient Characteristic	**In a Trial *n*=37 *n* (%)**	**Not a in Trial *n*=315 *n* (%)**	***P*-value**
Demographic Characteristics			
Age, yrs, mean±SD	55.94±25.04	55.94±8.48	1.000
Male gender	83.43 (50.00%)	83.43 (50.00%)	1.000
Income >$31,000	67.23 (45.76%)	79.70 (54.24%)	0.178
Married	116.2 (50.01%)	116.1 (49.99%)	0.994
Health Insurance	157.0 (50.00%)	157.0 (50.00%)	1.000
Education, yrs, mean±SD	13.59±7.60	13.9±2.57	1.000
Race/Ethnicity			
White	135.1 (50.00%)	135.1 (50.00%)	1.000
Black	19.16 (50.00%)	19.16 (50.00%)	1.000
Hispanic	14.25 (50.00%)	14.25 (50.00%)	1.000
Asian	7.45 (60.43%)	4.88 (39.57%)	0.456
Religion			
Catholic	65.83 (50.00%)	63.83 (50.00%)	1.000
Protestant	21.37 (50.00%)	21.37 (50.00%)	1.000
Baptist	17.17 (46.15%)	20.04 (53.85%)	0.619
Pentecostal	3.89 (61.78%)	2.41 (38.22%)	0.551
Jewish	22.21 (50.00%)	22.21 (50.00%)	1.000
Muslim	5.45 (58.33%)	3.89 (41.67%)	0.606
None	8.04 (38.52%)	12.83 (61.48%)	0.279
Recruitment Site			
Yale Cancer Center	81.34 (50.00%)	81.34 (50.00%)	1.000
Veterans Affairs CCC	0.00 (0.00%)	3.48 (100.00%)	0.061
Simmons Cancer Center	20.36 (50.43%)	20.01 (49.57%)	0.954
Parkland Hospital	29.36 (50.00%)	29.36 (50.00%)	1.000
DFCI/MGH	4.57 (31.01%)	10.18 (68.99%)	0.136
New Hampshire Oncology	18.78 (50.00%)	18.78 (50.00%)	1.000
Clinical Characteristics			
Cancer Type			
Lung	20.39 (50.00%)	20.39 (50.00%)	1.000
Pancreatic	33.41 (50.00%)	33.41 (50.00%)	1.000
Colon	19.66 (50.83%)	19.02 (49.17%)	0.912
Gastric	8.31 (50.00%)	8.31 (50.00%)	1.000
Esophageal	9.91 (50.00%)	9.91 (50.00%)	1.000
Biliary	0.00 (0.00%)	4.64 (100.0%)	0.030

	Enrollment in a Clinical Trial at Baseline		
Patient Characteristic	**In a Trial *n*=37 *n* (%)**	**Not a in Trial *n*=315 *n* (%)**	***P*-value**
Brain	8.47 (50.00%)	8.47 (50.00%)	1.000
Performance status, mean ± SD			
Karnofsky Score	68.95±41.09	68.77±13.79	0.925
ECOG Score	1.52±2.06	1.52±0.75	0.979
Charlson Comorbidity Index	7.58±5.29	7.58±1.93	1.000
McGill QOL, mean ± SD			
Sum Score	7.05±2.34	7.05±1.16	1.000
Physical function	5.89±4.23	5.53±2.06	0.162
Symptoms	5.86±3.40	5.86±1.64	1.000
Psychological	7.57±4.75	7.78±1.65	0.387
Support	8.51±3.37	8.71±1.37	0.253
Psychosocial Characteristics			
Brief COPE, mean ± SD			
Emotional support-based coping	2.00±1.34	1.86±0.67	0.095
Active coping	2.47±1.42	2.55±0.46	0.250
Behavioral disengagement	0.20±0.99	0.15±0.28	0.332
RCOPE, mean ± SD			
Positive RCOPE	10.09±15.42	9.55±4.87	0.449
Negative RCOPE	1.25±5.95	1.49±2.29	0.452
EOL Care Preferences and Advance Care Planning			
Terminal illness acknowledgement	59.82 (52.86%)	53.34 (47.17%)	0.459
Desires prognostic information	94.76 (48.68%)	99.92 (51.32%)	0.580
Prior EOL discussion	39.63 (50.00%)	39.63 (50.00%)	1.000
Preferences for EOL care			
Values life-extension over comfort	54.09 (44.44%)	67.62 (55.56%)	0.129
Against ICU death	58.30 (49.30%)	59.95 (50.70%)	0.853
Prefer ventilator	60.07 (54.48%)	50.18 (45.52%)	0.256
Prefer chemotherapy	156.5 (51.30%)	148.5 (48.70%)	0.214
Prefer feeding tube	67.50 (49.35%)	69.29 (50.65%)	0.845
DNR order	69.83 (50.97%)	67.19 (49.03%)	0.772
Living will & health care proxy	100.5 (50.28%)	99.33 (49.72%)	0.904

[a] *N*=352, decreased from 358 because of six patients with missing propensity score data.

Table 4

Adjusted Associations[a] of Clinical Trial Enrollment With EOL Care and QOL in the Last Week of Life in Propensity Weighted Analyses

End-of-Life Outcome		**Clinical Trial Experience**		**Unadjusted Analysis**		**Adjusted Analysis**	
Care in last week of life	**Total *N*=352 *n* (%)**	**Yes, *n*=37 *n* (%)**	**No, *n*=315 *n* (%)**	**OR/HR (95% CI)**	***P*-value**	**OR/HR (95% CI)**	***P*-value**
Aggressive EOL care[b]	46 (13.07%)	8 (21.6%)	38 (12.1%)	2.01 (0.86, 4.72)	0.108	2.04 (1.00, 4.15)	**0.050**
ICU admission	43 (12.22%)	8 (21.6%)	35 (11.1%)	2.20 (0.93, 5.19)	**0.072**	2.26 (1.09, 4.67)	**0.028**
Ventilator	26 (7.39%)	8 (21.6%)	18 (5.7%)	4.55 (1.82, 11.38)	**0.001**	8.22 (3.02, 22.40)	**<0.001**
Resuscitation	14 (3.98%)	2 (5.4%)	12 (3.8%)	1.48 (0.32, 6.89)	0.617	2.24 (0.63, 7.92)	0.210
Feeding tube	28 (7.95%)	7 (18.9%)	21 (6.7%)	3.22 (1.27, 8.20)	**0.014**	2.35 (0.95, 5.85)	**0.066**
Any hospice	250 (71.0%)	22 (59.5%)	228 (72.4%)	0.60 (0.29, 1.22)	0.160	0.82 (0.48, 1.42)	0.485
Hospice <1 week	152 (43.18%)	19 (51.4%)	133 (42.2%)	1.54 (0.77, 3.12)	0.225	1.96 (1.10, 3.50)	**0.023**
Procedures in last week of life[c]							
≥1 procedure	76 (21.6%)	14 (37.8%)	62 (19.7%)	2.48 (1.21, 5.10)	**0.013**	3.07 (1.71, 5.51)	**<0.001**
≥2 procedures	31 (8.8%)	8 (21.6%)	23 (7.3%)	3.50 (1.44, 8.53)	**0.006**	6.30 (2.50, 15.88)	**<0.001**
≥3 procedures	18 (5.1%)	5 (13.5%)	13 (4.1%)	3.36 (1.22, 10.84)	**0.021**	2.87 (0.91, 9.09)	0.072
Location of death[d]							
Hospital death	99 (28.13%)	18 (48.6%)	81 (25.7%)	2.74 (1.37, 5.47)	**0.004**	2.12 (1.24, 3.60)	**0.006**
ICU death	26 (7.4%)	6 (16.2%)	20 (6.3%)	2.85 (1.06, 7.62)	**0.037**	3.53 (1.29, 9.65)	**0.014**
Home death	199 (56.5%)	14 (37.8%)	185 (58.7%)	0.42 (0.21, 0.86)	**0.017**	1.30 (0.77, 2.22)	0.327
QOL in last week of life	Mean (SD)	LS Mean (SE)	LS Mean (SE)	*t*-value	*P*-value	*t*-value	*P*-value
Global quality of life[e]	6.32 (2.97)	5.93 (1.16)	7.68 (1.16)	1.22	0.223	−4.17	**<0.001**
Physical distress[f]	3.95 (3.5)	8.18 (1.35)	4.99 (1.34)	−1.60	0.110	6.72	**<0.001**
Psychological distress f	3.26 (3.17)	5.17 (1.22)	2.29 (1.21)	−2.20	**0.028**	6.58	**<0.001**

[a] For binary outcomes, the analyses were weighted by the normalized propensity score, and controlled for age, gender, education, race, biliary cancer, phase of trial and the patient's individual propensity score. For continuous outcomes, the analysis was controlled the same baseline characteristics and the five strata of the propensity score, and was weighted by the normalized propensity score.

[b] Aggressive EOL care: ICU stay, ventilator use, or resuscitation in the last week of life.

[c] ICU admission, ventilator, resuscitation, chemotherapy, or feeding tube in last week of life.

[d] Percentages do not add to 100% because of deaths located in nursing homes or inpatient hospice.

[e] Range 0–10, higher score indicates better QOL.

[f] Range 0–10, higher score indicates more distress.