

## Original Article

# An Individualized, Interactive Intervention Promotes Terminally Ill Cancer Patients' Prognostic Awareness and Reduces Cardiopulmonary Resuscitation Received in the Last Month of Life: Secondary Analysis of a Randomized Clinical Trial



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## Abstract

**Context/Objective.** Half of advanced cancer patients do not have accurate prognostic awareness (PA). However, few randomized clinical trials (RCTs) have focused on facilitating patients' PA to reduce their life-sustaining treatments at end of life (EOL). To address these issues, we conducted a double-blinded RCT on terminally ill cancer patients.

**Methods.** Experimental-arm participants received an individualized, interactive intervention tailored to their readiness for advanced care planning and prognostic information. Control-arm participants received a symptom-management educational treatment. Effectiveness of our intervention in facilitating accurate PA and reducing life-sustaining treatments received, two secondary RCT outcomes, was evaluated by intention-to-treat analysis using multivariate logistic regression.

**Results.** Participants ( $N = 460$ ) were randomly assigned 1:1 to experimental and control arms, each with 215 participants in the final sample. Referring to 151–180 days before death, experimental-arm participants had significantly higher odds of accurate PA than control-arm participants 61–90, 91–120, and 121–150 days before death (adjusted odds ratio [95% CI]: 2.04 [1.16–3.61], 1.94 [1.09–3.45], and 1.93 [1.16–3.21], respectively), but not one to 60 days before death. Experimental-arm participants with accurate PA were significantly less likely than control-arm participants without accurate PA to receive cardiopulmonary resuscitation (CPR) (0.16 [0.03–0.73]), but not less likely to receive intensive care unit care and mechanical ventilation in their last month.

**Conclusion.** Our intervention facilitated cancer patients' accurate PA early in their dying trajectory, reducing the risk of receiving CPR in the last month. Health care professionals should cultivate cancer patients' accurate PA early in the terminal-illness trajectory to allow them sufficient time to make informed EOL-care decisions to reduce CPR at EOL. *J Pain Symptom Manage* 2019;57:705–714. © 2019 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.

## Key Words

Prognostic awareness, life-sustaining treatments, blinded randomized clinical trial, end-of-life care, neoplasms

Trial registration: ClinicalTrials.gov:NCT01912846.  
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Accepted for publication: January 2, 2019.

## Introduction

Accurate prognostic awareness (PA) enables patients to make informed end-of-life (EOL)-care decisions,<sup>1,2</sup> thus reducing aggressive treatments and improving EOL-care quality.<sup>2,3</sup> However, far more cancer patients desire to know their prognosis (78.6%–96.9%) than physicians disclose it (7.0%–75.6%),<sup>4–6</sup> and approximately half of advanced/terminally ill cancer patients in a systematic review did not have accurate PA.<sup>7</sup> These statistics indicate the need for interventions to facilitate physicians' prognostic disclosure to promote accurate PA and reduce aggressive treatments at EOL.

Indeed, few randomized clinical trials (RCTs)<sup>8–14</sup> have examined the effectiveness of interventions in facilitating accurate PA<sup>8–12</sup> and reducing life-sustaining treatments (LSTs) at EOL<sup>8,13,14</sup> with only one<sup>8</sup> evaluating its effect on both outcomes, despite the well-established futility of LSTs in preserving terminally ill patients' life.<sup>15,16</sup> Furthermore, all these studies had insufficiencies in research design and outcomes.<sup>8–14</sup> Prognostic disclosure is advised to be tailored to patients' readiness/preparedness for receiving prognostic information,<sup>17</sup> a suggestion that was considered in guiding these studies,<sup>8–12</sup> but only two<sup>8,12</sup> explicitly assessed participants' readiness for prognostic information before providing their interventions. No studies were at least double blinded,<sup>8–14</sup> and treatment fidelity was neglected or underreported.<sup>9–14</sup> Most studies measured/reported patients' PA only once<sup>8,11</sup> or twice,<sup>9,12</sup> without evaluating the evolution of PA as death approached,<sup>8–12</sup> despite evidence that closer to death, patients may gradually realize their prognosis<sup>18–21</sup> from their aggravated symptoms<sup>6</sup> and more physicians disclosing prognosis.<sup>22</sup> To address these shortcomings, we analyzed the secondary outcomes of a blinded RCT of an individualized, interactive advanced care planning (ACP)<sup>23</sup> intervention in facilitating terminally ill cancer patients' accurate PA to reduce LSTs received in their last month. We hypothesized that tailoring our intervention to participants' readiness for prognostic information would facilitate cancer patients' accurate PA earlier in their terminal illness trajectory, thereby reducing LSTs received in their last month.

## Methods

### Overview

In this study, we analyzed secondary outcomes of a blinded RCT of a theory-based, tailored, multifaceted, interactive ACP intervention<sup>24</sup> (Supplement 1). The intervention was designed to increase congruence between patients' preferred and received EOL care, improve quality of life, lessen depressive and anxiety symptoms of patients and caregivers during the

patient's dying process, and enhance family caregivers' bereavement adjustment. We demonstrated that this intervention improved terminally ill cancer patients' psychological symptoms, but not their quality of life and preferred EOL care.<sup>24</sup> Herein, we report that intervention's effectiveness in two secondary outcomes, that is, facilitating patients' accurate PA and reducing LSTs received in the last month. Effectiveness of the ACP intervention in facilitating family caregivers' outcomes, physician-patient EOL-care discussions, and patient-caregiver agreement on EOL-care preferences has not been reported.

Dyads of terminally ill cancer patients and their primary family caregivers were randomly assigned 1:1 to the experimental (individualized, interactive intervention) and control (sham treatment of symptom-management education, with a similar format to that of the intervention) arms. To ensure blinding of arm assignment, the random allocation sequence was independently generated by a statistician or assigned by a researcher not involved in patient recruitment, interventions, and assessments. Data collectors were blinded to arm assignment. Experimental-arm interventionists and control-arm treatment providers were not blinded. No research staff were involved in clinical care. Detailed information has been reported about the study design, participant recruitment, treatments for each arm, and outcome assessments.<sup>24</sup> The RCT study protocol (Supplement 1) was approved by the ethics committee of the study site (101-0898A3) and registered at [ClinicalTrials.gov](http://ClinicalTrials.gov) (NCT01912846). All participants provided written informed consent before enrollment and randomization into study arms.

### Setting and Sample

Consecutive eligible adult oncology patients referred by their oncologists were recruited from April 2013 through June 2017 from a medical center in northwest Taiwan when their oncologist first recognized their cancer as terminal (metastatic disease continually progressed and was unresponsive to repeated chemotherapy/targeted therapies). Patients were excluded if they were diagnosed with psychiatric disorders, they were participating in other trials, they were under palliative care, or their family caregivers were unavailable/declined to participate. Of 795 patients approached, 460 (57.9%) were enrolled and randomly assigned 1:1 to the experimental and control arms (CONSORT diagram; Fig. 1). Primary reasons for declining participation were family caregivers' unavailability and patients' weakness.<sup>24</sup> Between-arm baseline characteristics, accurate PA, and LST preferences were balanced at randomization.<sup>24</sup>

### Sample Size

Sample size estimation for detecting a between-arm difference in one main outcome, concordance between

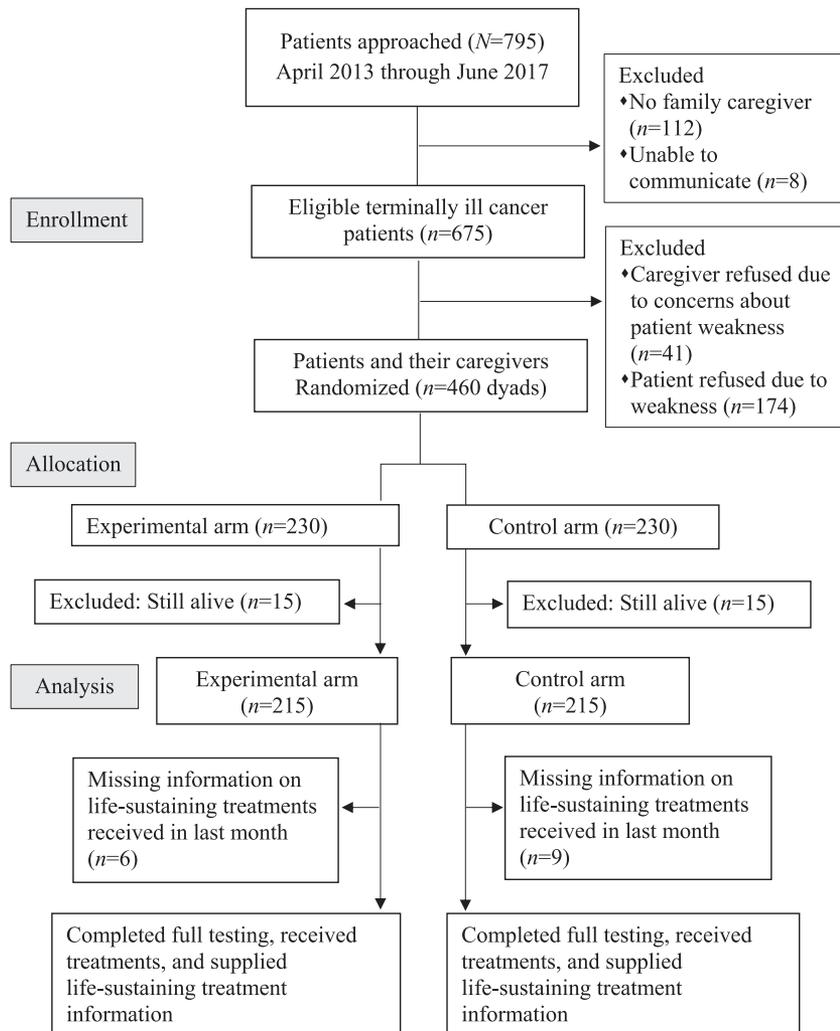


Fig. 1. CONSORT diagram.

patients' preferred and received LSTs, suggested a sample of 147–231 (Supplement 1). This sample size was adequate for detecting a between-arm difference in accurate PA (the primary outcome of this report) (86.1% power [two-sided testing,  $\alpha = 0.05$ ]) based on published effect sizes of 0.22–0.53 (average: 0.40),<sup>10</sup> considering the number of repeated measures ( $\geq 3$ )<sup>10</sup> and attrition rate (22%),<sup>10</sup> and adjusting for time-varying covariates, time proximity to death, and treatment dose (see Statistical Analysis section).

### Treatments

All participants in the experimental arm received a theory-based (the transtheoretical model),<sup>25</sup> tailored, multifaceted, interactive ACP intervention,<sup>24</sup> including 1) repeated assessments of participants' readiness to engage in ACP; 2) specific interventions tailored to participants' readiness to engage in ACP; 3) facilitating prognostic communication and EOL-care discussions among patients, family caregivers, and physicians; 4) using a booklet and video educational aid to

facilitate understanding of ACP and LSTs at EOL (Supplement 1); and 5) comforting participants while assessing their readiness to receive prognostic information and discussing EOL-care issues/concerns. Each intervention was provided by a trained, master's degree–prepared nurse with experience in oncology nursing and palliative care (detailed procedures for training experimental-arm interventionists and control-arm treatment providers are in Supplement 1), weekly during hospitalization or monthly at outpatient clinics when participants returned for visits, until they died. Participants in the experimental arm also received the same sham treatment as the control group (next paragraph).

Participants in the control arm received a sham treatment, including 1) symptom management provided by a trained, master's degree–prepared nurse with experience in oncology nursing and palliative care, weekly during hospitalization or monthly at outpatient visits until they died and 2) a booklet and video related to symptom management. This sham

treatment was based on a synthesis of seven systematic reviews that found using informative material alone did not promote ACP<sup>26</sup> and was designed to parallelize both study arms' education as much as possible.

### *Treatment Fidelity*

Treatment sessions were not audio-recorded or video-recorded for feasibility considerations, but after providing treatment components, interventionists for both arms recorded detailed information about these components to later evaluate compliance of treatment delivery with the study protocol. Compliance of experimental and sham treatment delivery according to protocol and assurance of treatment fidelity have been demonstrated.<sup>24</sup> Treatment fidelity was also ensured by confirming that the experimental treatment facilitated participants' transitions in PA toward accurate PA between the initial and final assessments (Supplement 2).

### *Outcome Measures*

PA was measured by asking patients whether they knew their prognosis, and if so, whether their disease 1) was curable; 2) might recur in the future, but their life was not currently in danger; and 3) could not be cured, or they would probably die soon.<sup>24</sup> Patients were recognized as accurately understanding their prognosis only if they chose Option 3. Patients were recognized as inaccurately understanding their prognosis if they did not know their prognosis or chose Option 1 or 2. This measure of PA was developed based on a literature review and Taiwanese physicians' cultural practice of prognostic disclosure. The validity of this measure is supported by its reflection of PA conceptualizations and measures used in a 34-study review of PA,<sup>7</sup> and its use showing that PA was significantly associated with physician-patient EOL-care discussions<sup>27</sup> and LST preferences<sup>28,29</sup> as well as quality of life, anxiety and depressive symptoms, and self-perceived burden to others<sup>19</sup> over terminally ill Taiwanese cancer patients' last year.

LSTs received in patients' last month, that is, cardiopulmonary resuscitation (CPR), intensive care unit (ICU) care, and mechanical ventilation, were retrieved from medical records and supplemented by family caregivers' reports during bereavement follow-ups.

### *Time-Varying Covariates*

For this longitudinal study, we adjusted for time-varying covariates shown to influence 1) patients' accurate PA, that is, desire for prognostic information,<sup>6,29</sup> physical symptom distress and functional dependence,<sup>6</sup> psychological symptoms<sup>30</sup>; and 2) receipt of LSTs at EOL, that is, LST preferences<sup>31</sup> and physical<sup>32</sup>/psychological symptom distress.<sup>33</sup>

Our time-varying variables reflect the nature of our longitudinal data, that is, each participant had subject-specific responses at different data collection times, and these responses likely differed between arms.<sup>34,35</sup> Detailed measures of each time-varying covariate are in Supplement 3.

### *Data Collection*

Data on participants' characteristics were collected at baseline (before random assignment). Data on outcome measures and time-varying covariates were collected by trained, experienced oncology nurses (Supplement 1) approximately every three to four weeks until participants declined participation or died. Data collectors were blinded to participants' arm allocation.

### *Statistical Analysis*

Intervention effectiveness was determined by intention-to-treat analysis.<sup>36</sup> To explore changes in accurate PA in patients' last six months,<sup>37</sup> time proximity to death (the period between death and assessment) was categorized as 1–30, 31–60, 61–90, 91–120, 121–150, and 151–180 days. Intervention effectiveness in facilitating accurate PA was examined by multivariate logistic regression by the generalized estimating equation (GEE).<sup>38</sup> GEE uses a working correlation structure to account for within-subject correlations of repeated observations from each patient. GEE allows different waves of data across patients to accommodate variable numbers of follow-up points, inconsistent time intervals between subsequent data collections, and missing data for the dependent variables. GEE uses all dependent variables available in each specific period to construct the model, thereby eliminating the need to delete observations in analyses or impute missing data.<sup>38</sup>

Because terminally ill cancer patients' accurate PA increases as death approaches,<sup>18–21</sup> we first examined the main effects of the intervention and time proximity to death (Model 1), and then examined the main effects and the interaction effect of "arm by time proximity to death" (Model 2).<sup>34,35</sup> Finally, we evaluated the effectiveness of our intervention in facilitating accurate PA for main effects and the interaction effect of "arm by time proximity to death," after adjusting for significant between-arm differences in baseline characteristics, time-varying covariates, and treatment dose (Model 3).<sup>34,35</sup> Treatment dose (number of treatments provided) and time-varying covariates were adjusted to account for different treatments received by each participant and different potential predictors of accurate PA (e.g., preference for prognostic information, symptom distress, functional dependency, and psychological symptoms)

experienced by each participant at each data collection time.<sup>34,35</sup>

To evaluate intervention effectiveness in reducing LSTs received in participants' last month by facilitating participants' accurate PA (a predefined hypothesis of the original study), we used multivariate logistic regression for the interaction effect of "arm by accurate PA" after adjusting for time-varying covariates and treatment dose. PA, time-varying covariates, and treatment dose in the last wave of assessment were adjusted in this analysis. The regression parameter for each independent variable was exponentiated to transform into adjusted odds ratio (AOR) with 95% CI. Statistical analyses were conducted using SPSS (Version 22.0).

## Results

### *Patient Characteristics*

Detailed baseline characteristics, accurate PA, and LST preferences for the final sample of 215 participants/arm who died by the end of the study, are given in [Table 1](#). Experimental- and control-arm participants received on average 5.99 ACP (SD = 6.11) intervention sessions and 5.40 (SD = 6.45) sham-treatment sessions, respectively. Postenrollment survival was 147.33 (SD = 155.01) and 127.39 (SD = 151.66) days for the experimental and control arms, respectively. After enrollment, experimental- and control-arm participants were assessed 5.19 (SD = 4.75) and 4.93 (SD = 5.35) times, respectively. The last assessment was on average 27.69 days (SD = 52.99) before death. Between-arm homogeneity in baseline and postenrollment characteristics was well established, except for the time spent in treatment/session ([Table 1](#)).

### *Intervention Effectiveness in Facilitating Accurate Prognostic Awareness*

Proportions of participants with accurate PA in the experimental arm generally increased as death approached, whereas the control arm's prevalence of accurate PA fluctuated ([Table 2](#)). Our results from multivariate logistic regression with GEE first showed significant main effects for "arm" (AOR [95% CI]: 1.45 [1.00–2.09],  $P = .048$ ) and "time proximity to death" on accurate PA ([Table 3](#), Model 1). Then, the interaction effect between "time proximity to death" on accurate PA without adjusting for time-varying covariates showed that experimental-arm participants had significantly and marginally higher odds of accurate PA than control-arm participants 61–90 (1.73 [1.04–2.87]), 121–150 (AOR [95% CI]: 1.83 [1.13–2.95]), and 91–120 (1.68 [0.99–2.86],  $P = 0.055$ ) days before death, respectively, with reference to 151–180 days before death (Model 2). Finally, after adjusting for time-varying covariates,

time proximity to death, and treatment dose, the odds of accurate PA, with reference to 151–180 days before death, were significantly higher in the experimental than in the control arm (AOR [95% CI]: 2.04 [1.16–3.61], 1.94 [1.09–3.45], and 1.93 [1.16–3.21]) for 61–90, 91–120, and 121–150 days before death, respectively ([Table 3](#), Model 3), but not for 1–60 days before death.

### *Our Intervention Reduced CPR Received in Participants' Last Month by Facilitating Accurate Prognostic Awareness but Did Not Impact Receipt of Other LSTs*

Experimental- and control-arm participants received comparable LSTs in their last month (4.8% vs. 4.9% for CPR, 8.7% vs. 7.3% for ICU care, and 10.6% vs. 7.3% for mechanical ventilation, respectively). However, the likelihood of receiving CPR in the last month, determined by multivariate logistic regression analysis, was significantly lower for experimental-arm participants with accurate PA (AOR [95% CI]: 0.16 [0.03–0.73],  $P = .019$ ) than for control-arm participants without accurate PA ([Table 4](#)), after adjusting for the last assessment of time-varying covariates and treatment dose. Between-arm likelihood of receiving ICU care and mechanical ventilation did not differ.

## Discussion

Our individualized, interactive intervention tailored to terminally ill cancer patients' readiness for prognostic information effectively facilitated accurate PA earlier in the terminal illness trajectory than for the control arm at 121–150, 91–120, and 61–90 days before death. This result is consistent with a report<sup>9</sup> that a decision aid improved prognostic understanding for patients with advanced colorectal cancer. However, our results were more effective in facilitating accurate PA than those using decision aids,<sup>12</sup> question-prompt lists and individualized communication coaching,<sup>8</sup> and early palliative care.<sup>10,11</sup> In one 6-month study,<sup>10</sup> more patients who received early palliative care maintained or developed accurate PA than those in the control arm, but between-arm accurate PA did not differ significantly at 12, 18, and 24 weeks after enrollment.

The effectiveness of our intervention in facilitating the development of terminally ill cancer patients' accurate PA early in their illness trajectory (61–150 days before death) can be attributed to several factors. First, our interactive intervention was tailored to patients' readiness for prognostic information. The desire for prognostic information has been advocated as key for accurate PA.<sup>6,26</sup> When we identified participants who did not know but wanted to know their prognosis, we encouraged them to discuss

Table 1  
Between-Arm Homogeneity for Participants (N = 430)

| Variable                                      | Experimental Arm (n = 215) | Control Arm (n = 215) | P                  |
|---|----------------------------|-----------------------|--------------------|
| Age, n (%)                                    |                            |                       | 0.129              |
| ≤54   | 85 (39.5)                  | 65 (30.2)             |                    |
| 55–64   | 76 (35.3)                  | 87 (40.5)             |                    |
| ≥65   | 54 (25.1)                  | 63 (29.3)             |                    |
| Gender, n (%)                                 |                            |                       | 0.341              |
| Male  | 156 (72.6)                 | 147 (68.4)            |                    |
| Female  | 59 (27.4)                  | 68 (31.6)             |                    |
| Marital status, n (%)                         |                            |                       | 0.983              |
| Married                                       | 179 (83.6)                 | 180 (83.7)            |                    |
| Not married                                   | 35 (16.4)                  | 35 (16.3)             |                    |
| Educational level, n (%)                      |                            |                       | 0.433              |
| ≤Junior high school                           | 123 (57.2)                 | 131 (60.9)            |                    |
| >Junior high school                           | 92 (42.8)                  | 84 (39.1)             |                    |
| Financial status, n (%)                       |                            |                       | 0.813              |
| Sufficient                                    | 166 (88.3)                 | 161 (87.5)            |                    |
| Insufficient                                  | 22 (11.7)                  | 23 (12.5)             |                    |
| Cancer diagnosis, n (%)                       |                            |                       | 0.772              |
| Liver   | 44 (20.5)                  | 53 (24.7)             |                    |
| Gastrointestinal                              | 43 (20.0)                  | 48 (22.3)             |                    |
| Esophageal                                    | 35 (16.3)                  | 34 (15.8)             |                    |
| Pancreatic                                    | 35 (16.3)                  | 28 (13.0)             |                    |
| Lung  | 13 (6.0)                   | 14 (6.5)              |                    |
| Other   | 45 (20.9)                  | 38 (17.7)             |                    |
| Metastasis, n (%)                             |                            |                       | 0.674              |
| Yes   | 202 (94.0)                 | 204 (94.9)            |                    |
| No  | 13 (6.0)                   | 11 (5.1)              |                    |
| Comorbidities, n (%)                          |                            |                       | 0.410              |
| Yes   | 141 (65.6)                 | 145 (69.3)            |                    |
| No  | 74 (34.4)                  | 66 (30.7)             |                    |
| Time since diagnosis                          |                            |                       |                    |
| Mean (SD), months                             | 12.03 (15.51)              | 10.46 (13.47)         | 0.264              |
| SDS score, mean (SD)                          | 26.98 (6.72)               | 26.69 (7.07)          | 0.662              |
| ESDS score, mean (SD)                         | 28.28 (8.82)               | 27.37 (8.60)          | 0.282              |
| HADS-D score, mean (SD)                       | 11.70 (4.33)               | 11.69 (4.50)          | 0.994              |
| HADS-A score, mean (SD)                       | 6.16 (3.79)                | 6.41 (3.80)           | 0.495              |
| Accurate prognostic awareness, n (%)          |                            |                       | 0.053 <sup>a</sup> |
| Yes   | 127 (59.1)                 | 107 (49.8)            |                    |
| No  | 88 (40.9)                  | 108 (50.2)            |                    |
| Preference for prognostic information         |                            |                       |                    |
| Mean (SD)                                     | 2.88 (1.05)                | 2.71 (1.12)           | 0.100              |
| Median  | 3                          | 3                     |                    |
| LST preference                                |                            |                       |                    |
| CPR, n (%)                                    |                            |                       | 0.929              |
| Yes   | 72 (31.3)                  | 69 (30.0)             |                    |
| No  | 139 (60.4)                 | 143 (62.2)            |                    |
| Uncertain                                     | 19 (8.3)                   | 18 (7.8)              |                    |
| ICU admission, n (%)                          |                            |                       | 0.836              |
| Yes   | 90 (39.3)                  | 94 (40.9)             |                    |
| No  | 121 (52.8)                 | 121 (52.6)            |                    |
| Uncertain                                     | 18 (7.9)                   | 15 (6.5)              |                    |
| Mechanical ventilation support, n (%)         |                            |                       | 0.598              |
| Yes   | 71 (30.9)                  | 66 (28.7)             |                    |
| No  | 143 (62.2)                 | 152 (66.1)            |                    |
| Uncertain                                     | 16 (7.0)                   | 12 (5.2)              |                    |
| Survival after enrollment, days               |                            |                       | 0.178              |
| Mean (SD)                                     | 147.33 (155.01)            | 127.39 (151.66)       |                    |
| Median (range)                                | 86 (5–689)                 | 79 (1–802)            |                    |
| Number of assessments after enrollment        |                            |                       | 0.580              |
| Mean (SD)                                     | 5.19 (4.75)                | 4.92 (5.34)           |                    |
| Median (range)                                | 3 (1–25)                   | 3 (1–33)              |                    |
| Number of treatments from enrollment to death |                            |                       | 0.326              |
| Mean (SD)                                     | 5.99 (6.11)                | 5.40 (6.45)           |                    |
| Median (range)                                | 4 (0–33)                   | 3 (0–46)              |                    |
| Time spent in treatment/session, minutes      |                            |                       | 0.001              |
| Mean (SD)                                     | 10.81 (4.29)               | 9.43 (3.31)           |                    |
| Median (range)                                | 10.16 (5.00–33.75)         | 9.81 (5.00–20.00)     |                    |

SDS = Symptom Distress Scale; ESDS = Enforced Social Dependency Scale; HADS-D = Hospital Anxiety and Depression Scale–Depression; HADS-A = Hospital Anxiety and Depression Scale–Anxiety; LST = life-sustaining treatments; CPR = cardiopulmonary resuscitation; ICU = intensive care unit.

<sup>a</sup>Between-arm difference in accurate PA approached statistical significance, but the effect size (Cohen's d = 0.187) was <0.2.

**Table 2**  
**Prevalence of Accurate Prognostic Awareness vs. Time Proximity to Death**

| Time Proximity to Death, Days | Experimental Arm |                                 | Control Arm    |                                 |
|-------------------------------|------------------|---------------------------------|----------------|---------------------------------|
|                               | n <sup>a</sup>   | Accurate PA, n (%) <sup>a</sup> | n <sup>a</sup> | Accurate PA, n (%) <sup>a</sup> |
| 1–30                          | 201              | 153 (76.1)                      | 199            | 136 (68.3)                      |
| 31–60                         | 164              | 116 (70.7)                      | 176            | 108 (61.4)                      |
| 61–90                         | 123              | 84 (68.3)                       | 136            | 79 (58.1)                       |
| 91–120                        | 102              | 75 (73.5)                       | 105            | 62 (59.1)                       |
| 121–150                       | 85               | 56 (65.9)                       | 88             | 49 (55.7)                       |
| 151–180                       | 81               | 50 (61.7)                       | 62             | 39 (62.9)                       |

<sup>a</sup>Number of assessments made by participants who could provide data. Some participants were interviewed more than once, and others could not be interviewed.

this desire with their physicians, thereby promoting physicians’ willingness to disclose the prognosis to patients,<sup>39</sup> and subsequently facilitating patients’ accurate PA.<sup>40</sup> The effectiveness of this intervention in facilitating physician prognostic disclosure to participants was validated by the between-arm comparison of physicians’ prognostic disclosure. The experimental arm had higher odds of physician prognostic disclosure than the control arm (AOR [95% CI]: 1.60 [1.13–2.26], *P* = .009) (Supplement 4). In addition, by repeatedly assessing participants’ readiness for prognostic information, our interventionists could clarify any prognostic misunderstandings, thereby promoting their accurate PA.

However, despite both arms showing increasing accurate PA in the last 60 days before death (Table 2), accurate PA in this period did not differ significantly between arms in our final GEE model (Table 3, Model 3), as reported.<sup>10</sup> Patients may develop accurate PA from perceiving their physical deterioration as death approaches.<sup>6</sup> Besides, physicians tend to delay prognostic disclosure till patients start to deteriorate physically or curative treatments are no longer effective,<sup>39</sup> as we validated by analyzing physician prognostic disclosure by time proximity to death (Supplement 4). Physicians were significantly more likely to disclose prognosis to participants in both arms at 1–30 and 31–60 days before death (AOR [95% CI]: 1.81 [1.23–2.66] and 1.48 [1.04–2.12], respectively) than 151–180 days before death. Therefore, in the last 60 days when death becomes apparent, participants in both arms had similar odds of developing accurate PA.

Our intervention reduced the likelihood of receiving CPR in the last month for experimental-arm participants by facilitating their development of accurate PA. Our individualized, interactive intervention more effectively limited use of CPR than providing advanced cancer patients with question-prompt lists and individualized consultation.<sup>8</sup> Because our experimental-arm participants developed accurate PA earlier (61–150 days before death) than control-arm participants, they may have had more time to prepare for death (emotionally and practically), thereby

**Table 3**  
**Multivariate Analyses of Intervention Effectiveness in Facilitating Accurate Prognostic Awareness (N = 430)**

| Variable                                    | Model 1          |                  | Model 2          |              | Model 3 <sup>a</sup> |              |
|---|------------------|------------------|------------------|--------------|----------------------|--------------|
|   | AOR (95% CI)     | <i>P</i>         | AOR (95% CI)     | <i>P</i>     | AOR (95% CI)         | <i>P</i>     |
| Intercept                                   | 0.97 (0.67–1.39) | 0.856            | 1.24 (0.81–1.88) | 0.327        | 0.43 (0.20–0.91)     | 0.027        |
| Experimental arm                            | 1.45 (1.00–2.09) | <b>0.048</b>     | 0.96 (0.53–1.75) | 0.902        | 0.83 (0.44–1.56)     | 0.563        |
| Control arm                                 | Ref              |                  | Ref              |              | Ref                  |              |
| Time proximity to patient death, days       |                  |                  |                  |              |                      |              |
| ≤30   | 2.35 (1.68–3.29) | <b>&lt;0.001</b> | 1.84 (1.16–2.92) | 0.009        | 1.00 (0.59–1.72)     | 0.996        |
| 31–60                                       | 1.66 (1.21–2.29) | <b>0.002</b>     | 1.28 (0.83–1.97) | 0.266        | 0.85 (0.52–1.39)     | 0.522        |
| 61–90                                       | 1.16 (0.90–1.50) | 0.253            | 0.85 (0.59–1.23) | 0.392        | 0.64 (0.42–0.97)     | 0.037        |
| 91–120                                      | 1.28 (0.98–1.68) | 0.074            | 0.95 (0.66–1.35) | 0.763        | 0.78 (0.53–1.14)     | 0.200        |
| 121–150                                     | 1.16 (0.90–1.49) | 0.256            | 0.83 (0.62–1.10) | 0.188        | 0.75 (0.55–1.02)     | 0.067        |
| 151–180                                     | Ref              |                  | Ref              |              | Ref                  |              |
| Arm × time proximity to patient death, days |                  |                  |                  |              |                      |              |
| Experimental arm × ≤30                      |                  |                  | 1.50 (0.78–2.90) | 0.225        | 1.80 (0.85–3.80)     | 0.124        |
| Control arm × ≤30                           |                  |                  | Ref              |              | Ref                  |              |
| Experimental arm × 31–60                    |                  |                  | 1.55 (0.83–2.91) | 0.169        | 1.92 (0.96–3.86)     | 0.066        |
| Control arm × 31–60                         |                  |                  | Ref              |              | Ref                  |              |
| Experimental arm × 61–90                    |                  |                  | 1.73 (1.04–2.87) | <b>0.036</b> | 2.04 (1.16–3.61)     | <b>0.014</b> |
| Control arm × 61–90                         |                  |                  | Ref              |              | Ref                  |              |
| Experimental arm × 91–120                   |                  |                  | 1.68 (0.99–2.86) | 0.055        | 1.94 (1.09–3.45)     | <b>0.025</b> |
| Control arm × 91–120                        |                  |                  | Ref              |              | Ref                  |              |
| Experimental arm × 121–150                  |                  |                  | 1.83 (1.13–2.95) | <b>0.014</b> | 1.93 (1.16–3.21)     | <b>0.011</b> |
| Control arm × 121–150                       |                  |                  | Ref              |              | Ref                  |              |
| Experimental arm × 151–180                  |                  |                  | Ref              |              | Ref                  |              |
| Control arm × 151–180                       |                  |                  | Ref              |              | Ref                  |              |

AOR = adjusted odds ratio; Ref = reference; SDS = Symptom Distress Scale; ESDS = Enforced Social Dependency Scale; HADS-D = Hospital Anxiety and Depression Scale–Depression; HADS-A = Hospital Anxiety and Depression Scale–Anxiety.

Bold indicates significant difference.

<sup>a</sup>Model 3: Preferences for prognostic information, SDS, ESDS, HADS-D, HADS-A, and treatment dose were controlled in multivariate logistic regression models with the generalized estimating equation.

Table 4  
Intervention Effectiveness in Reducing Life-Sustaining Treatments Received in the Last Month by Facilitating Accurate PA (N = 430)

| Variable                             | Cardiopulmonary Resuscitation |              | Intensive Care Unit Care |       | Mechanical Ventilation |       |
|--------------------------------------|-------------------------------|--------------|--------------------------|-------|------------------------|-------|
|                                      | AOR (95% CI)                  | P            | AOR (95% CI)             | P     | AOR (95% CI)           | P     |
| Intercept                            | 0.08 (0.01–0.61)              | 0.015        | 0.21 (0.03–1.37)         | 0.102 | 0.20 (0.04–1.01)       | 0.052 |
| Experimental arm                     | 0.55 (0.13–2.38)              | 0.424        | 0.79 (0.20–3.16)         | 0.734 | 0.86 (0.24–3.16)       | 0.825 |
| Control arm                          | Ref                           |              | Ref                      |       | Ref                    |       |
| Accurate PA                          |                               |              |                          |       |                        |       |
| Yes                                  | 0.28 (0.06–1.20)              | 0.085        | 0.43 (0.13–1.41)         | 0.163 | 0.58 (0.18–1.81)       | 0.345 |
| No                                   | Ref                           |              | Ref                      |       | Ref                    |       |
| Arm × accurate PA                    |                               |              |                          |       |                        |       |
| Experimental arm with accurate PA    | 0.16 (0.03–0.73)              | <b>0.019</b> | 0.64 (0.20–2.03)         | 0.451 | 0.58 (0.19–1.81)       | 0.346 |
| Experimental arm without accurate PA | 0.55 (0.15–2.03)              | 0.369        | 0.79 (0.21–2.94)         | 0.720 | 0.86 (0.25–3.04)       | 0.820 |
| Control arm with accurate PA         | 0.28 (0.06–1.30)              | 0.103        | 0.43 (0.13–1.47)         | 0.178 | 0.58 (0.18–1.82)       | 0.349 |
| Control arm without accurate PA      | Ref                           |              | Ref                      |       | Ref                    |       |

PA = prognostic awareness; AOR = adjusted odds ratio; Ref = reference; SDS = Symptom Distress Scale; ESDS = Enforced Social Dependency Scale; HADS-D = Hospital Anxiety and Depression Scale–Depression; HADS-A = Hospital Anxiety and Depression Scale–Anxiety.

Preferences for life-sustaining treatments, SDS, ESDS, HADS-D, HADS-A, and treatment dose were controlled in multivariate logistic regression. Bold indicates significant difference.

reducing the risk of receiving CPR.<sup>41</sup> Indeed, more of our experimental-arm participants with accurate PA than control-arm participants without accurate PA signed a do-not-resuscitate order in the last month (AOR [95% CI]: 2.26 [1.02–5.01],  $P = .043$ ) (data not shown), which reduces the likelihood of patients receiving CPR before death.<sup>42</sup> By contrast, if experimental-arm participants did not develop accurate PA before death, their likelihood of receiving CPR was not significantly lower than that of participants in the control arm. These results validate our hypothesis that tailoring our intervention to participants' readiness for prognostic information would facilitate cancer patients' accurate PA earlier in their terminal-illness trajectory, thereby reducing LSTs received in their last month.

However, our intervention did not reduce the receipt of ICU care and mechanical ventilation in terminally ill cancer patients' last month, consistent with the literature.<sup>8,13,14</sup> Unexpected medical problems may increase the chance of receiving ICU care at EOL.<sup>32</sup> Our experimental- and control-arm participants had similar life-threatening symptoms for ICU admission in their last month, including dyspnea (46.7% vs. 61.5%) or sepsis (33.3% vs. 30.8%) ( $P = .594$ , data not shown). Patients receiving chemotherapy or targeted therapy near EOL may also have a greater risk of receiving ICU care or mechanical ventilation support.<sup>43</sup> Indeed, a majority of our participants in the experimental and control arms received their last chemotherapy or targeted therapy within 30 days before receiving ICU care (61.5% vs. 58.3%,  $P = .870$ ) or mechanical ventilation support (57.1% vs. 60.0%,  $P = .889$ ) in the last month.

#### Study Strengths and Limitations

The strengths of this study include its interactive intervention tailored to participants' readiness for prognostic

information and its rigorous blinded design to ensure internal validity. However, our study had several limitations. It was conducted at a single hospital with a consecutively recruited sample of terminally ill cancer patients who had a primary family caregiver available and were referred by their oncologist, limiting generalization of the findings to national and international target populations without family caregivers. Indeed, patients with lung cancer and aged  $\geq 65$  years were substantially underrepresented in our sample. Furthermore, results from our measure of PA warrant further validation in other cultures and health care practices. Our findings also need to be validated to avoid Type I errors from multiple comparisons across the three LSTs. Using odds ratios to evaluate the effectiveness of our intervention in facilitating accurate PA (a common outcome with prevalence rate ranges of 61.7%–76.1% and 55.7%–68.3% for the experimental and control arms, respectively; Table 2) may inflate the estimated treatment effect, especially in studies with small samples.<sup>44</sup> However, this bias might have been mitigated in our study because each arm had over 200 participants. In addition, readiness to receive prognostic information was only assessed in the experimental arm. Therefore, we could not examine whether initial readiness to receive this information was related to either the outcome of accurate PA or receiving LSTs in the last month. However, our further analyses on experimental-arm participants only showed that our intervention facilitated participants moving from precontemplation/contemplation/preparation stages to the action/maintenance stage according to the transtheoretical model (Supplement 2). Furthermore, participants who moved to the action/maintenance stage earlier in their terminal-illness trajectory (two to six months before death) were significantly less likely than those who did so only in the last month to receive CPR, supporting our hypothesis that “tailoring our

intervention to participants' readiness for prognostic information would facilitate cancer patients' accurate PA earlier in their terminal-illness trajectory, thereby reducing LSTs received in their last month." Besides, we focused on patient participants and did not consider family caregivers' perspectives, despite the well-recognized power of Asian families in prognostic disclosure<sup>45</sup> and EOL-care decision making.<sup>46</sup> The attitudes of family caregivers will be fully explored in a future study for their impact on our intervention effectiveness in facilitating patient accurate PA to reduce aggressive LSTs and achieve value-concordant EOL care.

### Conclusion and Clinical Implications

Our interactive intervention tailored to cancer patients' readiness for prognostic information facilitated their accurate PA earlier in their terminal-illness trajectory than for the control arm, thus reducing likelihood of them receiving futile CPR in the last month. Our results provide health care professionals insight to cultivate terminally ill cancer patients' accurate PA by assessing their readiness for prognostic discussions early in the terminal illness trajectory, appropriately responding to their concerns, and clarifying prognostic misunderstandings and overexpectations of LST efficacy at EOL. Facilitating terminally ill patients' development of accurate PA earlier in the terminal illness trajectory allows them sufficient time to consider their EOL-care goals and prepare, emotionally and practically, for their EOL-care decision making. In this way, patients may make informed EOL-care decisions, avoid unnecessary suffering from aggressive LSTs, and achieve a value-concordant good death.<sup>47</sup>

### Disclosures and Acknowledgments

The authors have no financial or other conflict of interest to disclose.

This study was funded by National Health Research Institutes (NHRI-EX106-10208PI), Ministry of Science and Technology (MOST 104-2314-B-182-027-MY3), and Chang Gung Memorial Hospital (BMRP888).

No funding source had any role in designing and conducting the study; collecting, managing, analyzing, and interpreting the data; or preparing, reviewing, or approving the manuscript.

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## Appendix

### Supplement 1. Study Protocol

**Title:** An Interactive Advance Care Planning Intervention to Facilitate a Good Death for Cancer Patients.

**Brief summary:** The purpose of this five-year intervention study is to design, implement, and evaluate the effectiveness of an intervention aimed at facilitating prognostic communication and end-of-life (EOL) care decision making to increase congruence between patients' preferred and received EOL care, improve patients' and family caregivers' quality of life (QOL) and psychological well-being, reduce utilization of futile aggressive health care resources at EOL, and facilitate bereavement adjustment.

**Detailed description:** A randomized controlled trial of a tailored, multifaceted intervention will be conducted on a consecutively recruited sample of 231 dyads of terminally ill cancer patients and their family caregivers. Intervention effectiveness will be evaluated by comparing outcomes between patient-caregiver dyads in the experimental arm and the same number of dyads in a symptom-management education control arm.

The primary objectives are to examine the extent to which the proposed advanced care planning (ACP) intervention will 1) increase congruence between terminally ill cancer patients' preferred and received end-of-life (EOL) care; 2) improve quality of life (QOL) and reduce patients' and caregivers' depressive and anxiety symptoms during the patient's dying process; and 3) enhance family caregivers' bereavement adjustment.

The secondary objectives are to determine the effectiveness of the proposed ACP intervention in facilitating patients' prognostic awareness and EOL-care discussions among patients, families, and physicians; in increasing patient-caregiver agreement on EOL-care preferences; and in reducing aggressive EOL-care treatments for terminally ill cancer patients.

**Sample size calculation:** Sample size will be estimated based on observational evidence that EOL-care discussions between terminally ill cancer patients and their physicians increase congruence between patients' preferred and received EOL care.<sup>1</sup> This evidence was used because no intervention to date has been shown to directly increase congruence between terminal cancer patients' preferred and received EOL care. Patients who reported having EOL-care discussions with their physicians were more likely than those who did not have such discussions to receive EOL care consistent with their preferences (odds ratio [OR] = 2.04;  $P < .0001$ )<sup>1</sup> and received significantly fewer aggressive medical interventions near death, with lower rates of cardiopulmonary resuscitation (0.8% vs. 6.7%; adjusted odds ratio [AOR], 0.16; 95% CI, 0.03–0.80), mechanical ventilation support (1.6% vs. 11.0%; AOR, 0.26; 95% CI, 0.08–0.83), and intensive care unit care (4.1% vs. 12.4%; AOR, 0.35; 95% CI, 0.14–0.90). A sample of 124–190 dyads per arm would achieve 85% power to detect a between-arm difference in patient-physician EOL-care discussions by two-sided tests with  $P < .05$ . To compensate for the 18.5% attrition rate found in our previous longitudinal study,<sup>2</sup> 147–231 dyads per arm are needed. The proposed sample will target 231 dyads per arm to ensure adequate power to detect the hypothesized effects of the proposed intervention.

**Participant recruitment:** Terminally ill cancer patients will be consecutively referred by their participating oncologists by these criteria: 1) diagnosed with a terminal-stage disease that continues to progress with distant metastases and judged by their oncologists as unresponsive to current curative cancer treatment, 2) cognitively competent, 3) able to communicate with data collectors, 4) age >20 years, and 5) having a designated family caregiver who agrees to participate.

Family caregivers will be recruited if they 1) are family members of cancer patients with a terminally ill disease as defined by this proposed study, 2) are identified by patients as the primary person caring for them without financial reimbursement for that care, 3) age >20 years, and 4) agree to participate and can communicate with data collectors. Patients and family caregivers will be excluded if they participate in other research to facilitate prognostic awareness, ACP, QOL, or psychological well-being.

Detailed information about patients' eligibility criteria will be given to patients' oncologists who agree to participate in this study. They will be asked to identify and refer all dyads of patients and family caregivers without judging their emotional readiness to talk about their prognosis and EOL-care preferences. Referred patients' and caregivers' eligibility will be evaluated by data collectors who will invite them to participate in the study. Because QOL, depressive symptoms, and anxiety symptoms for both patients and family caregivers are primary study outcomes, patient-caregiver dyads will be excluded if either the patient or caregiver cannot communicate with the data collectors or refuses to participate.

Approximately 8–10 new dyads of terminally ill cancer patients and their family caregivers will be recruited each month. After developing a detailed study protocol, we will recruit the targeted 462 participant dyads (231 dyads in each treatment arm). We will enroll and randomly assign eligible patient-caregiver dyads 1:1 to the intervention or attention-control arm without stratification.

ACP intervention: The goal of this theory-based, tailored, multifaceted, interactive ACP intervention is to facilitate discussions among terminally ill cancer patients, their family caregivers, and their primary physicians about the patient's EOL-care preferences and to honor the patient's wishes. To that end, the ACP intervention will clarify each participant's understanding of the patient's prognosis and treatment options and her/his readiness to engage in ACP, help participants appropriately weigh the benefits and burdens of medical treatments at EOL, and clearly define and document the patient's preferences for their oncologist to use later to guide EOL-care decision making that honors the patient's preferences. The intervention constitutes dynamic and multiple interactions between patients, family caregivers, and primary physicians and a trained, master's degree-prepared ACP interventionist with experience in oncology nursing and palliative care. The ACP interventionist will use two decision aids (a booklet and a video) to enhance participants' understanding of the essential elements in ACP and aggressive EOL care.

The major components of the proposed ACP intervention will include 1) repeated assessments of participants' readiness to engage in ACP; 2) specific interventions tailored to participants' readiness to engage in ACP; 3) facilitating prognostic communication and EOL-care discussions among patients, family caregivers, and physicians; and 4) use of a booklet and a video educational aid to facilitate understanding of ACP and life-sustaining treatments at EOL.

The trained ACP interventionist will begin each course of the ACP intervention by independently and separately assessing each patient's and family caregiver's readiness to engage in ACP. The ACP interventionist will assess participants' understanding of how the illness is likely to progress, EOL-care preferences and goals, and readiness to engage in ACP. "Course" refers to each repetition of the four major intervention components. Each course will assess participants' readiness for ACP and EOL-care preferences to determine if they have changed over time and to adjust the intervention accordingly. The participant's stage of readiness to engage in ACP will be determined according to the Transtheoretical Model.<sup>3</sup> For this study, we propose that in the first stage, precontemplation, the participant is unaware of the prognosis or has no desire to engage in ACP planning. In the second stage, contemplation, the participant understands the relevance of ACP to his/her life and begins to consider his/her values and future treatment preferences. In the third stage, preparation, the participant commits to engage in ACP soon but is not yet ready to do so. In the fourth stage, action, the participant overtly engages in ACP, for example, discusses, and clarifies his/her EOL-care preferences with family members and health care professionals. In the fifth stage, maintenance, the participant has made EOL-care decisions and can periodically evaluate these decisions given changes in her/his life status.

The intervention protocol in this trial will not follow a script for discussing prespecified topics. Rather, the trained ACP interventionist will have the flexibility to provide participant-centered care tailored to the participant's specific needs at each stage of readiness to engage in ACP. For participants in the precontemplation stage, the goal of the individualized intervention will be to address participants' lack of readiness to engage in ACP and to motivate them to think of the relevance of ACP. For participants in the contemplation stage, the ACP interventionist will discuss life-sustaining treatments and palliative care that may be applicable to that patient, explain the benefits and burdens of each treatment, and encourage patients and caregivers to evaluate these benefits and burdens from their own perspective. For participants in the preparation stage, the ACP interventionist will help them to determine specific EOL-care preferences and to communicate their preferences and concerns to primary physicians. For participants ready to act on ACP, the ACP interventionist will communicate patients' and family caregivers' EOL-care preferences to their oncologist, thus facilitating EOL-care discussions to achieve a consensus on EOL-care goals and specific treatments that could be used or withheld. For participants who have made EOL-care decisions, the ACP interventionist will continually support and reassure them that their goals and EOL-care plan will be periodically reviewed based on changes in the patient's health status and preferences.

To enhance consensus in perceptions of the prognosis and EOL-care goals/preferences among terminally ill cancer patients, their family caregivers, and physicians, the ACP intervention protocol is designed to facilitate discussions about these topics throughout the dying process. Because patients' preferences and concerns fluctuate over the dying process, a basic tenet of this intervention is that ACP will be revisited periodically to ascertain any changes in participants' values regarding an acceptable QOL and desirable EOL care as the patient's death approaches. After the initial intervention course, the ACP interventionist will interact with participants at least every month until the patient dies. If the patient's health status declines as assessed by the primary physician or the patient experiences sentinel events, for example, initiating a new chemotherapy regimen, deciding to undergo major surgery, admission to an intensive care unit, initiating mechanical ventilation or new hemodialysis, and diagnosis with central nervous system metastases, the next intervention course will be scheduled immediately

to readdress the participant's EOL-care goals and preferences. The tailored intervention will be provided according to the patient's specific needs.

The symptom-management educational control arm is designed to compare the effects of the multifaceted, interactive ACP intervention to those of a symptom-management educational intervention to rule out the Hawthorne effect. The control-arm protocol will include prognostic disclosure and EOL-care discussions as needed according to current clinical practice. This study arm will be provided by treatment providers who are trained, master's degree—prepared nurses with experience in oncology nursing and palliative care. In the initial session for this arm, the treatment provider will give terminally ill cancer patients and family caregivers a booklet and a video with educational materials on how to manage common symptoms and a list of available resources, including patient support organizations, as well as support and financial assistance through the hospital's social work department. We hypothesize that using a booklet and video on symptom management alone will not impact the outcomes but will parallelize education received by the control arm as much as possible with that of the experimental arm. This hypothesis is based on a systematic review that found using informative material alone did not promote use of ACP.<sup>4</sup> The control-arm treatment provider will visit and interact with control-arm participants according to the same schedule as for the experimental arm (weekly during hospitalization or monthly at outpatient visits until they die) to assess their symptom distress and general well-being. Necessary referrals to physicians or social workers will be made for further management.

Data collection procedures: Participants will be assessed prospectively until patient death, loss to follow-up, study withdrawal, or when the patient can no longer be interviewed. Both patients and their family caregivers will be assessed every three weeks for QOL and other outcomes to cover the most rapid changes in patients' physical condition and demanding period of caregiving until the patient's death.<sup>5</sup> After each patient's death, his/her chart will be reviewed, and his/her caregiver will be interviewed to confirm the type of medical care received at EOL. At one, three, six, and 13 months after the patient's death, bereaved family caregivers will be interviewed. Thirteen months was chosen instead of 12 months to avoid contamination with effects based on anniversary grief reactions.<sup>6</sup>

Several strategies will be taken to ensure research fidelity.

1. Training of the treatment providers:

The proposed ACP intervention requires professionals skilled in the content, techniques, and delivery of the intervention. The interventionist will be trained using competency-based education based on her previous oncology and hospice care experiences. The training will include an overview of the study protocol and procedures, a review of the developed booklet and video, and instructions in motivational assessments. The interventionist will be coached by the principal investigator (PI), who will serve as a role model, to assess and motivate participants at different stages of readiness for engaging in ACP and cooperating with physicians to coordinate and facilitate EOL-care discussions. Before formal interventions can proceed, the interventionist will need to successfully demonstrate predefined competencies and consistency in delivering the ACP intervention after training and receiving individual feedback from the PI. Thereafter, the study team will meet biweekly to review the interventionist's notes on intervention sessions and to provide feedback on difficult participant-management issues.

The control-arm treatment provider will be trained by the PI to understand the purposes of this symptom-management educational treatment, how to assess common symptoms for terminally ill cancer patients, and how to use the booklet and video to help terminally ill cancer patients and their family caregivers manage the patient's symptom distress. During training, the treatment provider will receive individual feedback from the PI. Before the treatment provider can formally provide symptom-management educational treatment, she will need to successfully demonstrate competencies and consistency in delivering the treatment. Thereafter, the study team will meet periodically to review the treatment provider's notes on symptom-management educational treatment sessions and to provide feedback on difficult participant-management issues.

2. Interventions provided to experimental-arm participants will be compared every three months with those received by control-arm participants. Randomly selected patient-caregiver dyads in each treatment arm will be interviewed by the PI to check the extent to which treatments provided to them are consistent with the protocol for each arm.
3. To avoid bias, separate data collectors will be hired and trained to independently collect data for the experimental and control arms. These research assistants (RAs) will be blinded to treatment condition and trained to screen participants, obtain consent, and administer the project instruments without offering information. Procedures will be implemented to ensure that data collection is standardized. RAs' reliability will be established by comparing data collected by the RAs with that recorded by the PI on five pilot cases. PI-RA agreement must be 95% before RAs can collect data for the main study. Failure to reach this agreement rate will require additional training until the reliability level is acceptable. To maintain 95% PI-RA agreement, the PI will check reliability intermittently throughout the study.

4. To ensure continuing patient safety as well as the validity and scientific merits of the trial, an independent Data and Safety Monitoring Board (DSMB) will be organized. The DSMB will constitute a biostatistician experienced in statistical methods for clinical trials, a nurse researcher experienced in conducting randomized controlled trials, and a physician-scientist experienced in cancer care.

The DSMB will monitor and address the following issues: 1) sufficient and appropriate enrollment of participants, including compliance with the eligibility criteria for each dyad of terminally ill cancer patients and family caregivers enrolled in the trial; 2) appropriate implementation of randomization; 3) comparability of baseline data between treatment arms; 4) protocol compliance, including treatments delivered to each treatment arm and data collection schemes; 5) adverse events (AEs), quality assurance for data validation, and registry procedures for Clinical Trial registration at [ClinicalTrials.gov](http://ClinicalTrials.gov).

Treatments delivered to participants assigned to the intervention and symptom-management education arms will be compared every six months by interviewing randomly selected patient-caregiver dyads in each treatment arm to check treatment components provided to them.

The study team will record AEs and submit them in writing to the DSMB monthly, with immediate reporting of serious AEs to the DSMB and an oncologist with expertise in cancer care. Site-reported AEs/SAEs to its institutional review board will be dictated by local requirements.

No data will be analyzed before the study ends. Access to interim results, including results according to study arm, will be limited to DSMB members and the statistician who prepares the reports. The DSMB will review study data every six months, and the DSMB summary recommendations will be directed to the PI. A summary of the review of reported AEs/SAEs will be sent to the local institutional review board to ensure that the participating center will be informed of any pertinent safety issues.

The biostatistician will be responsible for ensuring quality of data submitted to the registry against the predefined range of each independent and dependent variable as well as for assessing the accuracy and completeness of registry data by comparing the submitted data to the original data.

#### Data analysis and interpretation

1. All data will be scored and entered into a computer spreadsheet by an administrative assistant blinded to participants' arm allocation.
2. To test for baseline equivalence among participants in each arm, between-arm differences in baseline characteristics and identified outcomes will be assessed with two-sided Fisher's exact tests and chi-square tests for categorical variables and independent-sample Student's t-tests for continuous variables.
3. Intervention effectiveness will be examined using intention-to-treat regression analyses with generalized estimating equations (GEEs). In the intention-to-treat regression analyses, all patient participants will be analyzed in the treatment arm to which they are initially allocated until they die, regardless of whether they complete or withdraw from the treatment.
4. Congruence between terminally ill cancer patients' preferred and received EOL care will be determined by comparing agreement between EOL-care preferences elicited at the last assessment and EOL care received by the patient. Congruence will be expressed by the percentage of overall agreement and kappa coefficients to correct for the extent of agreement expected to occur by chance alone.
5. The impact of the intervention on congruence between terminally ill cancer patients' preferred and received EOL care and on secondary outcomes (prognostic awareness, EOL-care discussions, patient-caregiver agreement on EOL-care preferences, use of futile aggressive EOL care, hospice use, and early hospice referral) will be determined by multivariate logistic regression using GEE, while adjusting for confounding factors. We will also use the GEE model to examine the moderation effects of prognostic awareness, EOL-care discussions, and patient-caregiver agreement on EOL-care preferences on between-arm differences in congruence between terminally ill cancer patients' preferred and received EOL care, use of futile aggressive EOL care, hospice use, and early hospice referral.
6. Intervention effects on patients' and family caregivers' QOL and psychological well-being (anxiety and depression), as well as family bereavement outcomes (including QOL, depression, and grief reactions) will be examined by multivariate multiple regression using the GEE with simultaneous adjustment for confounding factors. We will also use the GEE model to examine the moderation effects of prognostic awareness, EOL-care discussions, and patient-caregiver agreement on EOL-care preferences on between-arm differences in patients' and family caregivers' QOL and psychological well-being before the patient's death, as well as family bereavement outcomes. The GEE model will also be used to examine how the intervention's effectiveness on patients' and family caregivers' QOL and psychological well-being before the patient's death and family bereavement outcomes will be moderated by aggressive EOL care and congruence between terminally ill cancer patients' preferred and received EOL care.

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*Supplement 2*

**Transitions in Prognostic Awareness From the Initial to the Final Assessment Among Terminally Ill Cancer Patients in the Experimental Arm (N = 192)**

| Initial Assessment, <i>n</i> (%) | Final Assessment |         |           |            |           | Total                    |
|----------------------------------|------------------|---------|-----------|------------|-----------|--------------------------|
|                                  | I <sup>a</sup>   | II      | III       | IV         | V         |                          |
| I                                | 7 (3.6)          | 0 (0)   | 19 (9.9)  | 62 (32.3)  | 15 (7.8)  | 103 (53.6)               |
| II                               |                  | 1 (0.5) | 1 (0.5)   | 7 (3.6)    | 2 (1.0)   | 11 (5.7)                 |
| III                              |                  |         | 4 (2.1)   | 37 (19.3)  | 6 (3.1)   | 47 (24.5)                |
| IV                               |                  |         |           | 18 (9.4)   | 13 (6.8)  | 31 (16.1)                |
| V                                |                  |         |           |            | 0 (0)     | 0 (0)                    |
| Total                            | 7 (3.6)          | 1 (0.5) | 24 (12.5) | 124 (64.6) | 36 (18.8) | 192 (100.0) <sup>b</sup> |

<sup>a</sup>I–V represent the five stages of readiness to receive prognostic information according to the transtheoretical model as precontemplation, contemplation, preparation, action, and maintenance stage.

<sup>b</sup>Died before reevaluation (*n* = 23); McNemar's test, *P*-value < 0.001.

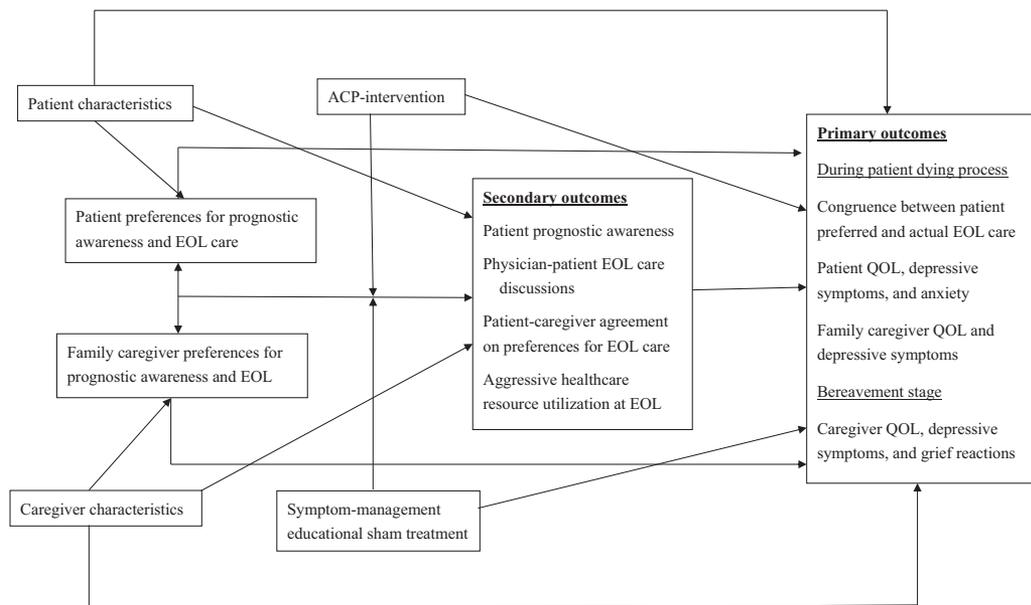
*Supplement 3*  
**Measurement of Time-Varying Covariates**

| Instrument  | Characteristics  | Scoring  |
|---|--|--|
| Preference for physicians' prognostic disclosure <sup>7</sup> | Single-item, self-report scale asks patients to rate their degree of desire for prognostic information.  | Items are scored on a five-point Likert scale (1 = strongly not prefer; 5 = strongly prefer). Desire for prognostic information was dichotomized at the median score into want to know (>3) and do not want to know (<3).  |
| Life-sustaining treatment (LST) preferences <sup>8,9</sup>    | Self-report scale, using an adapted interview protocol, <sup>8,9</sup> asking patients three questions (see scoring) to assess preferences for cardiopulmonary resuscitation (CPR) when life is in danger, intensive care unit (ICU) care, and intubation with mechanical ventilation.   | For each LST, patients are asked whether they 1) want the treatment, 2) do not want the treatment, or 3) are undecided. Patients' LST preferences were dichotomized into "want treatment" and "do not want treatment," with "undecided" responses counted as wanting the treatment because the clinical default in most instances is to provide treatment unless specifically refused. <sup>10</sup> |
| Preference for CPR  | Patients were asked whether they wanted CPR when life was in danger (if their heart or breathing stopped). CPR comprises a combination of electric shocks to the heart, pumping the chest to stimulate the heart, placing a tube through the mouth or nose into the lungs, and attaching this tube to a breathing machine to help with breathing, and heart medications given through the veins. |  |
| Preference for ICU admission                                  | Patients were asked whether they wanted to stay in an ICU when they needed intensive care. An ICU is an isolated care unit that heavily uses health technology to provide intensive care and their family only had contact with them at specific visiting times.   |  |
| Preference for mechanical ventilation support                 | Patients were asked whether they want to be intubated and on a breathing machine when they are unable to breathe on their own.   |  |
| Symptom Distress Scale (SDS) <sup>11</sup>                    | A 13-item, self-report scale with 11 symptoms, asking patients to rate the degree, frequency, and intensity of symptom distress, including nausea, appetite, insomnia, pain, fatigue, bowel pattern, concentration, appearance, breathing, outlook, and cough  | Items are scored on a five-point Likert scale (1 = no distress; 5 = extreme distress). Total scores range from 13 to 65, with higher scores indicating greater distress.   |
| Enforced Social Dependency Scale (ESDS) <sup>12</sup>         | A 10-item, self-report scale, asking patients to rate their dependence on external sources to carry out duties that are ordinarily taken for granted, such as eating, walking, and bathing.  | A Likert scale of 3 to 6 points. Total scores range from 10 to 51, with higher scores reflecting greater dependence on assistance for personal and social functioning.   |
| Hospital Anxiety and Depression Scale (HADS) <sup>13</sup>    | A 14-item scale with two 7-item subscales (anxiety and depression), asking patients to rate items according to how they have felt during the previous week.  | Items are scored from 0 to 3. Total subscale scores range from 0 to 21, with higher scores indicating more severe depression or anxiety. A score of 0–7 indicates no anxiety/depression, 8–10 indicates mild anxiety/depression, 11–14 indicates moderate anxiety/depression, and 15–21 indicates severe anxiety/depression.   |

*Supplement 4*  
**Between-Arm Comparison of Physicians' Prognostic Disclosure (N = 430)**

| Variable                      | B     | Wald $\chi^2$ | AOR (95% CI)     | P      |
|-------------------------------|-------|---------------|------------------|--------|
| Intercept                     | -1.12 | 32.66         | 0.33 (0.22-0.48) | <0.001 |
| Experimental arm              | 0.47  | 6.90          | 1.60 (1.13-2.26) | 0.009  |
| Control arm                   |       |               | Ref              |        |
| Time proximity to death, days |       |               |                  |        |
| ≤30                           | 0.59  | 9.08          | 1.81 (1.23-2.66) | 0.003  |
| 31-60                         | 0.39  | 4.60          | 1.48 (1.04-2.12) | 0.032  |
| 61-90                         | 0.20  | 1.25          | 1.22 (0.86-1.71) | 0.263  |
| 91-120                        | -0.02 | 0.01          | 0.99 (0.72-1.35) | 0.925  |
| 121-150                       | -0.05 | 0.10          | 0.95 (0.68-1.32) | 0.749  |
| 151-180                       |       |               | Ref              |        |

AOR = adjusted odds ratio; Ref = reference.  
 Comparisons made by multivariate logistic regression models with the generalized estimating equation.



Conceptual Framework