Associations between Mild Cognitive Dysfunction and End-of-Life Outcomes in Patients with Advanced Cancer

Keiko Kurita, PhD, MPH,^{1,2} M. Cary Reid, MD, PhD,² Eugenia L. Siegler, MD,²
Eli L. Diamond, MD,³ and Holly G. Prigerson, PhD^{1,2}

Abstract

Background: Cognitive function of patients with advanced cancer is frequently compromised.

Objective: To determine the extent that patients' cognitive screening scores was associated with their end-of-life (EoL) treatment preferences, advance care planning (ACP), and care.

Design: Patients were interviewed at baseline and administered a cognitive screen. Caregivers completed a postmortem assessment.

Setting/Subjects: Patients with distant metastases and disease progression after first-line chemotherapy and their caregivers ($n = 609$) were recruited from outpatient clinics and completed baseline and postmortem assessments.

Measurements: In logistic regression models adjusting for patients' age, education level, and performance status, patients' scores on the Pfeiffer Short Portable Mental Status exam at baseline predicted ACP, treatments, and treatment preferences at baseline, and location of death and caregiver perceptions of the patients' death in a postmortem assessment.

Results: For each additional error, patients were less likely to consider the intensive care unit a bad place to die (adjusted odds ratio [AOR] = 0.81; confidence interval [95% CI]: 0.66–0.98; $p = 0.03$) and less likely to have an inpatient hospice stay (AOR = 0.63; 95% CI: 0.40–1.00; $p = 0.05$). After death ($n = 318$), caregivers were more likely to perceive that patients died at patients' preferred location (AOR = 1.38; 95% CI: 1.01–1.88; $p = 0.04$) and less likely to perceive that patients preferred to extend life over relieving discomfort (AOR = 0.63; 95% CI: 0.40–0.99; $p = 0.05$).

Conclusions: Patient cognitive screening scores were associated with EoL outcomes. Rather than avoid patients who are cognitively impaired, oncologists should consider ACP with them.

Keywords: cognitive dysfunction; end-of-life outcomes; patients with advanced cancer

Introduction

MILD COGNITIVE IMPAIRMENT is common in patients with advanced cancer.^{1,2} It increases as patients approach death due to disease progression, complications, and treatment.³ Therefore, it is important to understand the potential influence of mild cognitive impairment on patients' end-of-life (EoL) experience, particularly in the context of concurrent physical deterioration.^{4,5}

Little is known about associations between advanced cancer patients' cognitive dysfunction and EoL preferences and advance care planning (ACP). Associations between

patients' cognitive impairment or decline and completion of do-not-resuscitate (DNR) orders, less hospice use, and caregiver preferences for life-extending and intensive patient care have been found.^{4,6,7} Nevertheless, a study using a composite measure of poor cognitive performance and functional limitations found that it was not associated with treatments received or hospitalizations at EoL.⁸

We sought to determine the extent to which scores on a validated cognitive screen were associated with EoL treatment preferences, ACP, and care for patients with advanced cancer, independent of the likely confounding influence of performance status.

¹Center for Research on End-of-Life Care, Weill Cornell Medicine, New York, New York.

²Division of Geriatrics and Palliative Medicine, Department of Medicine, Weill Cornell Medicine, New York, New York.

³Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, New York.

Accepted November 9, 2017.

Methods

Sample

The sample was derived from Coping with Cancer, an NCI-funded, prospective, longitudinal cohort study of terminally ill patients with cancer and their informal, unpaid caregivers.⁹ Patients were recruited from eight cancer clinics across the Northeast and Southwest. Human subject committees at each participating center approved the study, and participants provided written informed consent.

Inclusion criteria were as follows: patients who had distant metastasis with disease progression after first-line chemotherapy; age ≥ 20 years; informal caregivers' participation; adequate stamina to complete the study; fluency in English or Spanish; and a score of fewer than 6 errors on the Short Portable Mental Status (SPMS) exam.¹⁰ In this study, we include patients for whom SPMS scores, age, years of education, and Karnofsky performance status¹¹ were available ($n = 609$).

Procedures

At baseline, a trained rater interviewed patients and administered the SPMS. Within three weeks of the patient's death, caregivers completed a postmortem assessment on patients' EoL experiences and staff conducted medical chart abstraction.

Measures

Primary independent variable. The SPMS is an easily administered, validated, 10-item screen for cognitive impairment that has been tested in clinical and institution-based samples. Test-retest reliability has been ≥ 0.82 , and the agreement between the SPMS and clinical diagnosis for intact cognition or mild impairment was 82%. Intact mental function refers to the respondent making 0 to 2 errors, and mild, moderate, and severe impairment as 3 to 4, 5 to 7, and 8 to 10 errors, respectively.¹⁰ Scoring was adjusted such that one additional error was allowed if the participant had only grade school education and one less error if the participant had education beyond high school. No adjustments were made if a participant made no errors. Thus, higher screening scores indicate worse functioning. The education-level adjusted number of cognitive errors was the main continuous, predictor variable.

Covariates. Participants self-reported their age and last grade completed in school. For education, participants were categorized into four groups: ≤ 6 years, 7 to 12 years, 13 to 16 years, and ≥ 17 years of formal schooling. Participants' physical performance status was assessed by trained clinicians using the Karnofsky Performance Score,¹¹ ranging from 100 (normal) to 0 (dead). Educational level was an ordinal variable, and age and performance status were continuous variables.

Dependent variables. At baseline, trained clinicians recorded patients' current treatments from medical records. These included analgesic medications given the high prevalence of pain in patients with advanced cancer.¹² Patients were asked whether they preferred "extending life as much as possible, even if it meant more pain and discomfort" or

"relieving pain and discomfort as much as possible, even if that meant not living as long"; had completed a DNR order; had signed a living will, healthcare proxy, and/or durable power of attorney for healthcare; considered death in an ICU versus elsewhere as "bad"; and acknowledged their current health status as terminally ill. At postmortem, inpatient hospice stay, outpatient hospice stay, and location of patients' death were recorded. In addition, caregivers were asked whether they thought that the patients' treatment preferences immediately before patients' deaths were to extend life or to relieve pain or discomfort and whether they thought the actual location of death was where the patient had preferred to die. Outcomes were analyzed as dichotomous measures.

Statistical analysis

Differences in group means and frequencies were compared by using *t*- and chi-square tests. Two logistic regression models examined the extent to which cognitive scores were associated with outcomes: an unadjusted, base model with only the main predictor, and an adjusted model with the main predictor and covariates that were significantly associated with the outcome at $p < 0.05$. SAS 9.4 was used, hypothesis tests were two sided, and $p < 0.05$ was considered statistically significant.

Results

The mean age of the analytic sample was 59 years (standard deviation = 13; Table 1). Approximately half of the participants graduated from high school and were female. On average, the sample was "able to care for self, but is unable to

TABLE 1. SAMPLE CHARACTERISTICS ($N = 609$)

	Mean (SD)	No.	Frequency %
Age, years	59.2 (13.1)		
Education, years	12.7 (3.9)		
Female ^a		309	50.8
Race/ethnicity ^a			
White		433	71.2
Black		92	15.1
Asian, Pacific Islander, Indian		8	1.3
Hispanic		73	12.0
Other		2	0.3
Karnofsky performance status score ^b	68.2 (16.3)		
Cognitive screening			
Errors	0.57 (0.9)		
Intact mental function			
0 errors		407	66.8
1 error		92	15.1
2 errors		83	13.6
Impairment			
3 errors		19	3.1
4 errors		7	1.1
5 errors		1	0.2

Cognitive status is measured by the Short Portable Mental Status. The number of errors was adjusted for years of education.

^aSex and race/ethnicity data were missing for one patient; based on $n = 608$.

^bKarnofsky score = 70 corresponds to "The patient is able to care for self, but is unable to do his or her normal activities or active work."

SD, standard deviation.

TABLE 2. ASSOCIATION BETWEEN PATIENT COGNITIVE ERRORS AND PATIENTS' CARE, END-OF-LIFE CARE PLANNING, AND PREFERENCES AT BASELINE (N=609)

Outcomes	Base model		Adjusted model	
	OR (95% CI)	p	OR (95% CI)	p
Is receiving chemotherapy ^a	0.72 (0.60–0.86)	<0.001	0.84 (0.69–1.01)	0.07
Is receiving radiation ^a	0.89 (0.60–1.30)	0.53	0.80 (0.54–1.20)	0.28
Is receiving pain medication ^a	1.51 (1.21–1.89)	<0.001	1.41 (1.11–1.78)	<0.001
Completed a do-not-resuscitate order ^b	1.20 (1.0–1.43)	0.05	1.13 (0.93–1.36)	0.23
Has a HCP, living will, or DPA ^c	0.95 (0.79–1.14)	0.57	0.93 (0.75–1.14)	0.46
Prefers to extend life over relieving pain or discomfort ^d	0.83 (0.66–1.04)	0.10	0.88 (0.70–1.11)	0.29
Acknowledges terminal illness ^e	1.22 (1.01–1.47)	0.03	1.16 (0.96–1.40)	0.13
Considers dying in ICU “bad” compared with home, hospice, or elsewhere ^f	0.81 (0.66–0.98)	0.03	0.81 (0.66–0.98)	0.03

In the adjusted models, covariates of age, education level, and Karnofsky Performance Score associated with the outcome at $p < 0.05$ are included. The following were included in the adjusted models (where cognitive errors were significant in the base models): all covariates for models predicting chemotherapy and pain medication; education level and Karnofsky scores for the model predicting terminal acknowledgment; and no covariates for the model predicting attitude for dying in the ICU.

Models did not include patients' responses that were missing or “do not know” and were based on the following sample sizes: ^a $n = 559$ (50 missing); ^b $n = 552$ (56 missing, 1 “do not know”); ^c $n = 548$ (49 missing, 12 “do not know”); ^d $n = 507$ (51 missing, 51 “do not know”); ^e $n = 533$ (75 missing, 1 “do not know”); ^f $n = 551$ (57 missing, 1 “do not know”).

CI, confidence interval; DPA, Durable Power of Attorney; HCP, health care proxy; ICU, intensive care unit; OR, odds ratio.

do his or her normal activities or active work,” and most had intact mental function. The postmortem interview occurred a median of four months after baseline for the 318 patients who died in the study observation period. Cognitive scores and survival from baseline to death were negatively associated ($r = -0.14$, $p = 0.02$).

For each additional cognitive error, the odds were 1.4 times greater that patients were receiving pain medication ($p < 0.001$), 1.2 times greater that patients did not consider dying in an ICU “bad” compared with home, hospice, or elsewhere ($p = 0.03$), and 1.6 times greater that patients did not have inpatient hospice stays in the last week of life ($p = 0.05$; Table 2). After the patient's death, for each additional cognitive error, caregivers were 1.6 times more likely to report that their family member's preference was to relieve pain and discomfort over extending life ($p = 0.05$) and 1.4

times greater to report that patients died in their preferred place of death ($p = 0.04$; Table 3).

Discussion

In this large, prospective study of patients with advanced cancer, worse patient cognitive screening scores were associated with their caregivers believing that they died where they wanted and that they preferred to relieve pain and discomfort over extending life. The association between cognitive impairment and acknowledgment of terminal illness lost statistical significance when physical deterioration and education level were included, suggesting that together, they may signal that death is near.

Associations between cognitive impairment and treatments received is understandable given that pain medications

TABLE 3. ASSOCIATION BETWEEN PATIENT COGNITIVE ERRORS AND PATIENTS' END-OF-LIFE EXPERIENCES AT FOLLOW-UP (N=318)

Outcomes	Base model		Adjusted model	
	OR (95% CI)	p	OR (95% CI)	p
Patient had inpatient hospice stay ^a	0.61 (0.38–0.97)	0.04	0.63 (0.40–1.00)	0.05
Patient had outpatient hospice stay	1.01 (0.79–1.28)	0.95	0.96 (0.75–1.22)	0.72
Patient's location of death was a hospital facility*	0.78 (0.60–1.00)	0.05	0.81 (0.62–1.04)	0.10
Caregiver believed that the patient's preference was to extend life over relieving pain ^b	0.61 (0.39–0.96)	0.03	0.63 (0.40–0.99)	0.05
Caregiver believed that actual location of death was the patient's preferred choice ^c	1.38 (1.01–1.88)	0.04	1.38 (1.01–1.88)	0.04

In the adjusted models, covariates of age, education level, and Karnofsky Performance Score associated with the outcome at $p < 0.05$ are included. The following covariates were included in the adjusted models (where cognitive errors were significant in the base models): education level for the model predicting inpatient hospice stay; patient's age for the model predicting caregivers' belief of patients' preference to relieve pain; and no covariates for model predicting caregivers' belief of patients' death location was preferred.

*Hospital facility included ICU unit, other hospital units, and inpatient hospice.

Models did not include patients' responses that were missing or “don't know” and were based on the following sample sizes: ^a $n = 317$ (1 missing); ^b $n = 309$ (9 “do not know”); ^c $n = 311$ (3 missing, 4 “do not know”).

may affect cognitive function. As previously shown, patients with poor performance status are less likely to receive chemotherapy.¹³ That said, there was a consistent preference for palliation as the focus of EoL care at both baseline and postmortem assessments. These results suggest that patients with cognitive impairment may be more receptive to palliative care and should be approached to discuss goals of care, as they can articulate their overall values and preferences, even if they cannot make complex treatment decisions. This is consistent with research that has shown that compared with cognitively intact older adults, patients with mild cognitive impairment also possess the capacity to make reasonable choices regarding the receipt of their own medical care.¹⁴ There is a need to understand better the role of cognitive status in shaping patient prognostic understanding, plans, and care, especially because research has demonstrated that EoL care is occasionally inconsistent with patient preferences and leaves many needs unmet.^{15,16} Similarly, the findings that worse cognitive screening scores of patients were associated with their caregivers' beliefs postmortem about the patients' EoL care suggest that caregivers' perceptions and beliefs may prevail if there is a conflict between the wishes of patients and their caregivers.^{7,17}

It bears repeating that this sample passed the cognitive screen for study participation. Thus, participants who scored in range above high-moderate to severe cognitive impairment were excluded. These findings highlight the influence of a narrow range of errors (the most common item that patients answered incorrectly was serial 3 subtraction from 20). Much additional research is needed to understand how the broader range of cognitive impairment affects patient EoL medical decision making.¹⁴ In practice, it may be beneficial for clinicians to recognize that cognitive impairment falls on a range from mild forms, which can go undetected, to severe, including dementia. EoL conversations should be tailored to match patients' cognitive capacity.

This study should be considered in light of its strengths and weaknesses. A strength of the study is that from a mostly mentally intact sample of patients with advanced cancer, cognitive scores with adjustments for performance status were shown to influence EoL experience. Our study was limited by use of a cognitive screen to assess cognitive dysfunction. Testing of specific cognitive domains may reveal additional findings. The sample of mostly white patients with advanced cancer may seem to limit generalizability of the findings. However, cancer is the second leading cause of death; so, examining the EoL experiences of cancer is highly relevant, and the proportion of the sample who were white is representative of the U.S. population.¹⁸ Future research on noncancer patient populations and more racially and ethnically diverse samples is needed to generalize these findings given how race and ethnicity may affect care received by patients with dementia.^{19,20}

Our results suggest that oncologists might consider the presence of mild cognitive impairment among advanced cancer patients as a reminder to have EoL discussions. EoL discussions should occur earlier in the course of illness. Conversations that occur later in illness may be in the context of worse patient cognitive function. Cognitive dysfunction should not result in avoidance of EoL conversations. Future studies are needed to examine the full range of cognitive capacity in patients and its influence on EoL choices and receipt of value-consistent care.

Acknowledgments

This study was supported by a grant from the National Cancer Institute and the National Institute of Mental Health (R01 CA106370 and R01 MH63892, awarded to H.G.P.). K.K. is supported by a grant from the National Institute on Aging (T32 AG049666). Dr. H.G.P. is supported by a grant from the National Cancer Institute (R35 CA197730). M.C.R. is supported by grants from the National Institute on Aging (P30 AG022845 and K24 AG053462) and the Howard and Phyllis Schwartz Philanthropic Fund. E.L.S. is an investigator on an approved investigator-initiated research grant from Gilead Sciences and receives support from the Fan Fox and Leslie R. Samuels Foundation.

Author Disclosure Statement

No competing financial interests exist.

References

- Ahles TA, Root JC, Ryan EL: Cancer- and cancer treatment-associated cognitive change: An update on the state of the science. *J Clin Oncol* 2012;30:3675–3686.
- Jean-Pierre P, McDonald BC: Neuroepidemiology of cancer and treatment-related neurocognitive dysfunction in adult-onset cancer patients and survivors. In: Rosano C, Ikram M, Ganguli M (eds.): *Neuroepidemiology. Handbook of Clinical Neurology*. Cambridge, MA: Elsevier, 2016, pp. 297–310.
- Batty GD, Deary IJ, Zaninotto P: Association of cognitive function with cause-specific mortality in middle and older age: Follow-up of participants in the English Longitudinal Study of Ageing. *Am J Epidemiol* 2016;183:183–190.
- Karikari-Martin P, McCann JJ, Farran CJ, et al.: Race, any cancer, income, or cognitive function. *Am J Hosp Palliat Med* 2015;33:537–545.
- Tolea MI, Morris JC, Galvin JE: Longitudinal associations between physical and cognitive performance among community-dwelling older adults. *PLoS One* 2015;10: e1022878.
- de Decker L, Annweiler C, Launay C, et al.: Do not resuscitate orders and aging: Impact of multimorbidity on the decision-making process. *J Nutr Health Aging* 2014;18: 330–335.
- Gao X, Prigerson HG, Diamond EL, et al.: Minor cognitive impairments in cancer patients magnify the effect of caregiver preferences on end-of-life care. *J Pain Symptom Manage* 2013;45:650–659.
- Koroukian SM, Schiltz NK, Warner DF, et al.: Social determinants, multimorbidity, and patterns of end-of-life care in older adults dying from cancer. *J Geriatr Oncol* 2017;8: 117–124.
- Wright AA, Zhang BH, Ray A, et al.: Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. *JAMA* 2008;300:1665–1673.
- Pfeiffer E: A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc* 1975;23:433–441.
- Yates JW, Chalmer B, McKegney FP: Evaluation of patients with advanced cancer using the Karnofsky performance status. *Cancer* 1980;45:2220–2224.
- van den Beuken-van Everdingen MH, Hochstenbach LM, Joosten EA, et al.: Update on prevalence of pain in patients

- with cancer: Systematic review and meta-analysis. *J Pain Symptom Manage* 2016;51:1070–1090.
13. Prigerson HG, Bao Y, Shah MA, et al.: Chemotherapy use, performance status, and quality of life at the end of life. *JAMA Oncol* 2015;1:778–784.
 14. Okonkwo OC, Griffith HR, Copeland JN, et al.: Medical decision-making capacity in mild cognitive impairment. *Neurology* 2008;71:1474–1480.
 15. Khandelwal N, Curtis JR, Freedman VA, et al.: How often is end-of-life care in the United States inconsistent with patients' goals of care. *J Palliat Med* 2017;20:1400–1404.
 16. Teno JM, Freedman VA, Kasper JD, et al.: Is care for the dying improving in the United States? *J Palliat Med* 2015; 18:662–666.
 17. Pope TM. Legal fundamentals of surrogate decision making. *Chest* 2012;141:1074–1081.
 18. National Center for Health Statistics. *Health, United States, 2016: With Chartbook on Long-term Trends in Health*. US Department of Health and Human Services, Centers for Disease Control and Prevention, Hyattsville, MD, 2017. <https://www.cdc.gov/nchs/data/abus/hos16.pdf> (last accessed December 27, 2017).
 19. Mitchell SL, Teno JM, Intrator O, et al.: Decisions to forgo hospitalization in advanced dementia: A nationwide study. *J Am Geriatr Soc* 2007;55:432–438.
 20. Mitchell SL, Mor V, Gozalo PL, et al.: Tube feeding in US nursing home residents with advanced dementia, 2000–2014. *JAMA* 2016;316:769–770.

Address correspondence to:

Holly G. Prigerson, PhD

Center for Research on End-of-Life Care

Weill Cornell Medicine

525 East 68th Street, Box 39

1414 Baker Pavilion

New York, NY 10065

E-mail: hgp2001@med.cornell.edu