Current status of advance care planning, palliative care consultation, and end-of-life care in patients with glioblastoma in South Korea

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Abstract

Background: Given the typical trajectory of glioblastoma, many patients lose decision-making capacity over time, which can lead to inadequate advance care planning (ACP) and end-of-life (EOL) care. We aimed to evaluate patients' current ACP and EOL care status.

Patients and Methods: We conducted a cohort study on 205 patients referred to oncologists at a Korean tertiary hospital between 2017 and 2022. We collected information on sociodemographic factors, cancer treatment, palliative care consultation, ACP, legal documents on life-sustaining treatment (LST) decisions, and aggressiveness of EOL care.

Results: With a median follow-up time of 18.3 months: 159 patients died; median overall survival: 20.3 months. Of the 159 patients, 11 (6.9%) and 63 (39.6%) had advance directive (AD) and LST plans, respectively, whereas 85 (53.5%) had neither. Among the 63 with LST plans, 10 (15.9%) and 53 (84.1%) completed their forms through self-determination and family determination, respectively. Of the 159 patients who died, 102 (64.2%) received palliative care consultation (median time: 44 days from the first consultation to death) and 78 (49.1%) received aggressive EOL care. Those receiving palliative care consultations were less likely to receive aggressive EOL care (83.3% vs 32.4%, *P* < .001), and more likely to use more than 3 days of hospice care at EOL (19.6% vs 68.0%, *P* < .001).

Conclusions: The right to self-determination remains poorly protected among patients with glioblastoma, with nearly 90% not self-completing AD or LST plan. As palliative care consultation is associated with less aggressive EOL care and longer use of hospice care, physicians should promptly introduce patients to ACP conversations and palliative care consultations.

Key words: end-of-life care; advance care planning; goal-concordant care; palliative care consultation; glioblastoma.

Implications for Practice

Key implications from this study emphasize the critical role of early advance care planning discussions and the integration of palliative care consultations in the management of patients with glioblastoma. Ensuring patients have self-completed advance directives and life-sustaining treatment plans is paramount. Health care providers must prioritize delivering goal-concordant care to improve end-of-life (EOL) outcomes. By implementing these strategies, clinicians can enhance the quality of care, minimize aggressive EOL interventions, and promote patient-centered practices in glioblastoma care.

Introduction

Glioblastoma, the predominant form of primary malignant brain tumor, displays remarkable aggressiveness, presenting a grim prognosis with a typical survival expectancy of only 15 months.^{1,2} It is a complex disease that burdens both patients and their caregivers, with high morbidity and complex symptoms. Common physical symptoms encompass headaches, nausea, vomiting, and profound fatigue, while neurological manifestations may include seizures, motor weakness, aphasia, vision impairment, cognitive deterioration, and psychiatric manifestations.³ According to the European Association of Neuro-Oncology (EANO) guidelines published in 2017 and updated in 2022, it is crucial and strongly advised to implement early palliative care interventions for establishing

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treatment objectives and reducing symptom distress in individuals diagnosed with glioblastoma.^{3,4} However, advance care planning (ACP) and end-of-life (EOL) care for these patients have been poorly performed,⁵ as most lose their decision-making capacity over the course of their disease,^{6,7} and data are lacking on how EOL care is actually being implemented in patients with glioblastoma.

The enactment of the Life-Sustaining Treatment Decisions Act occurred in 2018 in Republic of Korea, and the National Health Insurance Service began partially covering counseling and administrative tasks associated with life-sustaining treatment (LST) decisions concerning terminally ill patients. At any time they choose, adults have the opportunity to fill out an advance directive (AD) at national registry agencies, while individuals in the terminal stage of illness and during their final days can collaborate with their physicians to establish an LST Plan.⁸

This study aimed to evaluate the present status of palliative care consultation, ACP, and EOL care in patients with glioblastoma, and identify the factors associated with aggressive EOL care and goal-concordant care.

Materials and methods

Study population

This study was a retrospective study with 205 patients who had been diagnosed with glioblastoma and referred to oncologists at Seoul National University Bundang Hospital (SNUBH) in Korea between January 2017 and September 2022. Information on sociodemographic factors, cancer treatment, palliative care consultation, ACP (including legal documents on LST decisions), and the aggressiveness of EOL care were collected through medical chart review. The National Agency for Management of Life-Sustaining Treatment oversees the integration of all legal forms into the Life-Sustaining Treatment Information Processing System, which can be accessed at https://intra.lst.go.kr/login/pkiLogin.do. This system is interconnected across hospitals, ensuring that pertinent information regarding LST decisions is accessible within our institution even if the patient has completed legal documents elsewhere. Additionally, regarding hospice utilization, certified hospice nurses from registered medical institutions can verify whether the patient has used hospice services and the date of death. The Institutional Review Board of the SNUBH granted approval for this study (IRB No. B-2211-790-109) and the necessity for obtaining informed consent was waived. It was conducted according to the principles of the Declaration of Helsinki.

Definition of outcome variables

Legal documents on LST decisions include an AD or LST Plan, which is a type of Physician Orders for LST (POLST), completed by a physician at the disease's end stage. The LST Plan is completed by the patient (self-determination); however, family members can complete the form in case the patient loses decision-making capacity (family determination).

Regarding the definition of aggressive EOL care, we used the definition from the National Quality Forum and American Society of Clinical Oncology (ASCO) Quality Oncology Practice Initiative (QOPI). The ASCO QOPI measure refers to chemotherapy within the last 2 weeks of life⁹ and intensive care within the last 30 days of life¹⁰ as aggressive measures; furthermore, as an additional measure, it situates enrollment in hospice care for at least 3 days prior to death as an indicator of high-quality care.¹¹ Previous research indicates that early hospice care yields several benefits, including less aggressive care and higher-quality EOL care.^{12,13} Consequently, hospice care is widely recognized as a form of high-value, patientcentric care. Therefore, in this paper, aggressive EOL care was defined as chemotherapy in the last 14 days of life, intensive care in the last 30 days of life, and hospice care for 3 days or less.

Goal-concordant care was defined as EOL care according to AD and LST plans documented by patients, or LST plans documented by surrogate decision-makers knowing patients' preferences.

Statistical analysis

Continuous variables were depicted as median values, while categorical variables were represented as percentages (numbers). Comparison between categorical and continuous variables was conducted using chi-square and independent sample t-tests, respectively. The length of hospice stay and overall survival (OS) were calculated using the Kaplan-Meier method. Multivariate logistic regression analyses were performed to examine the predictors of palliative care consultations, hospice enrollment, aggressive EOL care, and goal-concordant care. The following variables were included: age at diagnosis (>60 or ≤60 years), sex (male or female), marital status (married or unmarried), level of education (≤middle school, high school, or \geq college), occupation (employed or unemployed), religion (yes or no), residence (rural/suburban or metropolitan areas), health insurance (National Health Insurance or Medical Aid), and scope of surgical intervention (biopsy/subtotal resection or gross total resection).

Significance was determined using a 2-sided test with a threshold of P < .05. Data analysis was performed using IBM SPSS Statistics for Windows, version 25.0 (Armonk, NY, USA) and GraphPad Prism 9 (GraphPad Software Inc, La Jolla, CA, USA).

Results

Patient characteristics and clinical outcomes

Table 1 shows the patients' characteristics. Their median age at diagnosis was 57.9 years (range: 19.8-82.5), and 109 (53.2%) of them were male. Most patients were married, lived in a metropolitan area, and had a high school diploma or higher. More than half of the patients practiced a religion, including Protestants (n = 40), Catholics (n = 35), Buddhists (n = 34), and others (n = 3). With a median follow-up time of 18.3 months (range: 3.3-136.8), 159 patients died, and the median OS was 20.3 months (95% CI, 17.5-23.1; Figure 1).

ACP status including legal documents on LST decision

Of 205 patients, 79 (38.5%) had AD or LST plans (Supplementary Table S1). Only 13 (6.3%) had AD; 66 (32.2%) had an LST plan, with 10 (4.9%) completing their own forms, and 56 (27.3%) patients' forms were completed by family members because they had lost their decision-making capacity.

Of the 159 deceased patients, 46.5% (74/159) had AD or LST plans (Table 2). Eleven (6.9%) patients had documented AD, and median time from AD documentation to death was 18.9 months (range: 5.5-41.6 months). Sixty-three (39.6%)

 Table 1. Baseline characteristics.

Variables	N (%)
Age, median (range)	57.9 (19.8-82.5)
Sex	
Male	109 (53.2)
Female	96 (46.8)
Marital status	
Married	165 (80.5)
Unmarried	38 (18.5)
Unknown	2 (1.0)
Education level	
<middle school<="" td=""><td>31 (15.1)</td></middle>	31 (15.1)
High school	75 (36.6)
≥College	96 (46.8)
Unknown	3 (1.5)
Religion	
No	91 (44.4)
Yes	112 (54.6)
Unknown	2 (1.0)
Occupation	
Unemployed	110 (53.7)
Employed	93 (45.4)
Unknown	2 (1.0)
Residence	
Rural/suburban	56 (27.3)
Metropolitan	159 (72.7)
Health Insurance	
National health insurance	199 (97.1)
Medical aid	6 (2.9)
Surgery	
Biopsy/STR	101 (49.3)
GTR	98 (47.8)
Not received	2 (2.0)
Unknown	4 (1.0)
Radiation therapy	
Received	202 (98.5)
Not received	3 (1.5)
Chemotherapy	
Received	202 (98.5)
Not received	3 (1.5)

Abbreviations: STR, Subtotal resection; GTR, Gross total resection.

patients had an LST plan, and the remaining 85 (53.5%) did not have either an AD or LST plan. Among the 63 patients with an LST plan, 10 (15.9%) completed the form by selfdetermination, whereas the remaining 53 (84.1%) completed it by family determination. Regarding surrogate decisionmaking by family members, preferences for LST were known for 34 (64.2%) patients. The largest proportion of surrogate decision-makers were linear descendants (sons and daughters, grandchildren; n = 39, 73.6%), followed by spouses (n = 36, 67.9%), linear ascendants (parents and grandparents; n = 14, 26.4%), and siblings (n = 3, 5.7%). In the remaining cases (35.8%, n = 19), the patient's preferences for LST were



Figure 1. Overall survival of patients with glioblastoma.

Table 2. Advanced care planning status in deceased patients (N = 159).

Advance care planning status	N (%)
LST plan not documented	85 (53.5)
LST plan documented	74 (46.5)
AD	11 (6.9)
LST plan, self-determination	10 (6.3)
LST plan, family determination, known patient's preference	34 (21.4)
LST plan, family determination, unknown patient's preference	19 (11.9)

Abbreviations: AD, advance directive; LST, life-sustaining treatment.

unknown, requiring a unanimous decision by all immediate family members.

EOL care and goal-concordant care status

Among the 159 deceased patients, 78 (49.1%) received aggressive EOL care (chemotherapy in the last 14 days of life, n = 2; intensive care in the last 30 days of life, n = 4; received hospice care for 3 days or less, n = 78). Eighty-six (54.1%) patients used hospice care, and 81 (50.9%) used more than 3 days of hospice care at the EOL. The median length of hospice stay was 34 days (95% CI, 26.6-41.4; Supplementary Figure S1). While the observed difference was not statistically significant (P = .078), patients who completed an AD or LST plan were less likely to receive aggressive EOL care than those who did not (42.5% vs 56.6%; Supplementary Table S2). A trend toward aggressive EOL care was also found, with 33.3% of patients having a self-written AD or LST plan, and 46.2% having an LST plan written by a family member, compared to 56.6% of patients with no AD or LST plans (P = .129; Table 3). Median time from AD/LST plan documentation to death was 6.4 months (range: 0.3-41.6 months) for patients with self-written AD/LST plan and 0.97 months for patients with LST plan written by family members (range: 0.0-5.7 months).

Among 55 patients with a self-completed AD or LST plan, or LST plan documented by family members knowing the patients' preferences, goal-concordant care was achieved in 33 (60%) patients.

Palliative care consultation and quality of EOL care

Palliative care consultations were conducted to manage distressing symptoms, provide counseling for patients and their families, facilitate readiness for hospice referrals, and prepare for EOL care, and were provided to 115 of the 205 (56.1%) patients. Among the 159 deceased patients, 102 (64.2%) had received palliative care consultations, and the median time from the first consultation to death was 44 days (range: 0-240.0). Palliative care consultation was associated with less aggressive EOL care; those who received palliative care consultations were less likely to receive aggressive EOL care (83.3% vs 32.4%, P < .001), and more likely to use more than 3 days hospice care at the EOL (19.6% vs 68.0%, P < .001), compared to those who did not receive palliative care consultations (Table 4). Subsequently, a multivariable logistic regression analysis was used to assess factors predicting the provision of aggressive EOL care, as those who were religious and receiving palliative care consultations were significantly less likely to receive aggressive EOL care (Table 5). Age, sex, education, residence, and having an AD or LST plan were not associated with the aggressiveness of EOL care.

When comparing the timing of palliative care consultations (>90 days before death, between 30 and 90 days, and within 30 days) with the length of stay in hospice care, it was found that the earlier the timing of palliative care consultation, the longer the length of stay in hospice care (median length of stay: 51 vs 38 vs 11 days, P < .001; Figure 2).

Palliative care consultation also had an impact on whether goal-matched care was achieved. Even in patients with an AD or LST plan (self-determination or family determination with known patients' preferences; n = 55), goal-concordant care was less likely to be achieved in patients who did not have palliative care consultation compared to those who did (16.7% vs 72.1%, P < .001).

The median time from documentation of AD/LST plan to death was 1.17 months (95% CI, 0.88-1.45). The median

Table 3. Relationship between AD/LST status and aggressive EOL care.

AD/LST status	Aggressive EOL care		P-value
	No	Yes	
AD/LST-self	14 (17.9)	7 (9.0)	.129
LST-family	28 (35.9)	24 (30.8)	
No AD/LST	36 (46.2)	47 (60.3)	

Abbreviations: AD, advance directive; LST, life-sustaining treatment; EOL, end-of-life.

 Table 4. Relationship between palliative care consultation and aggressive

 EOL care and hospice care.

EOL care	Palliative care consultation		P-value
	No	Yes	
Aggressive EO	L care		
No	9 (16.7)	69 (67.6)	<.001
Yes	45 (83.3)	33 (32.4)	
Hospice care m	nore than 3 days		
No	45 (80.4)	33 (32.0)	<.001
Yes	11 (19.6)	70 (68.0)	

Abbreviation: EOL, end-of-life.

 Table 5. Odds ratios and 95% CIs for potential predictors of aggressive

 EOL care in patients with glioblastoma.

Characteristics	Odd ratio (95% CI)	P-value
Age ≥ 60 (vs <60)	1.208 (0.518-2.821)	.662
Female (vs male)	0.982 (0.380-2.525)	.969
Unmarried (vs married)	1.321 (0.469-3.727)	.598
Level of education ≥ col- lege (vs ≤High school)	0.521 (0.220-1.232)	.138
Unemployed (vs employed)	0.704 (0.274-1.807)	.465
Having a religion (vs no religion)	0.435 (0.196-0.969)	.042
Metropolitan (vs rural/ suburban)	1.969 (0.762-5.091)	.162
Medical aid (vs NHI)	1.190 (0.102-13.836)	.889
GTR (vs biopsy/STR)	1.190 (0.517-2.740)	.683
AD/LST plan documen- tation (vs no)	0.956 (0.429-2.131)	.913
Palliative care consulta- tion (vs no consultation)	0.089 (0.034-0.229)	<.001

Abbreviations: EOL, end-of-life; NHI, National Health Insurance; STR, subtotal resection; GTR, gross total resection; AD, advance directive; LST, life-sustaining treatment.



Figure 2. Timing of palliative care consultation and length of stay in hospice.

time from AD/LST plan documentation to death for patients who received palliative care consultation was longer than that for patients who did not receive such consultations, but the difference was not statistically significant (1.33 months [95% CI, 1.09-1.58] vs 0.80 months [95% CI, 0.47-1.13], P = .738). The median time from completion of AD/LST planning documentation to death was longer for patients who received >3 days of hospice care compared to those who did not (1.37 [95% CI, 1.01-1.72] months vs 0.80 months [95% CI, 0.51-1.09]), but the difference was not statistically significant (P = .363).

Discussion

In this study, nearly 90% of patients with glioblastoma did not have a self-completed document on LST, and half of them received aggressive EOL care. Even among patients with an AD/LST plan (self-determination or family determination with known patients' preferences), 40% did not receive goal-concordant care, suggesting that documentation of an AD/LST plan alone was insufficient to ensure goalconcordant care. Palliative care consultation was provided to 64% of patients, who were less likely to receive aggressive EOL care and more likely to use hospice services for more than 3 days at EOL compared to patients with no palliative care consultation.

A person diagnosed with glioblastoma will experience a variety of symptoms, mostly of neurological origin. In a systematic review encompassing 32 studies, the most commonly reported symptoms were seizures, cognitive deficits, drowsiness, dysphagia, headache, confusion, aphasia, and motor deficits.¹⁴⁻¹⁶ Psychological symptoms also affect high-grade glioma. The median frequency of depression was 15% in a systematic review of 42 studies that included 4089 patients,¹⁷ and depression was linked to diminished physical functioning, cognitive decline, and a lower quality of life (QoL).¹⁸ For both patients and caregivers, the impact of high-grade glioma on daily life was severe, with the shock of the diagnosis and perception of death being the most challenging issues, followed by patients' coping with restrictions and loss of autonomy, and caregivers taking full responsibility for alterations in relationships stemming from neurocognitive symptoms and shifts in personality exhibited by patients.^{19,20}

According to the World Health Organization's definition, palliative care is a treatment that aims to improve the QoL for both patients and their families confronting difficulties associated with life-threatening illnesses. This can be achieved through early detection, accurate assessment and management of pain, and addressing physical, psychological, and spiritual issues.²¹ The timely incorporation of specialized palliative care into routine oncology care improves the QoL, mood, satisfaction, health care service use, and possibly survival in patients with advanced cancer.²²

Despite the high need for the early incorporation of palliative care in patients with glioblastoma, ACP and palliative care consultation are underutilized for them. A recent systematic review encompassing 16 nonrandomized studies from 6 countries found that ACP documentation rates for patients with glioblastoma ranged from 4% to 55%, palliative care referral rates from 39% to 40%, and hospice referral rates from 66% to 76%.²³ Similarly, this study found palliative care consultation and hospice referral rates of 64.2% and 54.1%, respectively.

Additionally, one of the implications of this study is that even in patients with an AD/LST plan (self-written or family decision with patients' preferences), 40% did not receive treatment that met their goals and received aggressive EOL care, meaning that their autonomy is still not adequately protected. However, this does not mean that AD/LST documentation is unimportant: in the majority of patients, LST plan documentation was completed by family members near the EOL (median time from LST plan documentation to death: 1.0 month), and these patients had high rates of aggressive EOL care despite LST plan documentation (46. 2%), while patients with self-created AD/LST plans had lower rates of aggressive EOL care (33.3%), given that, these plans were created earlier (median time from AD/LST plan documentation to death: 6.4 months). Together with previous findings of a gap between the goals of patients with cancer and their families, and the care patients actually receive,^{24,25} this study

Through enhanced outreach and educational efforts, ACP will progress toward maximizing respect for individual autonomy. The impact of provider training and cultural patterns on palliative care and EOL management is worth exploring. In a survey study analyzing practice patterns of palliative care utilization among attendees of a neuro-oncology annual meeting in North America, female gender, formal training in neuro-oncology and palliative care, and medical versus surgical neuro-oncology training were associated with hospice referral and comfort in dealing with EOL issues.²⁶ Participants with palliative care training through courses referred 60% of their patients to hospice for EOL cares, compared to only 45% of participants without formal training. In another survey, conducted jointly by the Society of Neuro-Oncology, European Association of Neuro-Oncology (EANO), and Asian Society of Neuro-Oncology, palliative care utilization patterns varied by region of the world. Physicians in the United States and Canada were more likely to refer patients to hospice compared to physicians in Asia-Oceania and Europe (63%, 8%, and 19%, respectively).²⁷ Since gender, region, or specialty (neurology/oncology vs neurosurgery) is not something that can be changed, increasing education and training in palliative care seems to be an important step that can make a difference. Effective ACP also relies on comprehensive communication between patients and health care providers. However, there is little compensation for investing time in ACP counseling, and physicians and other providers are often unable to devote time to communication due to heavy clinical workloads. Therefore, increasing staffing and funding for palliative care can help ensure quality ACP delivery.

Another point to emphasize in the EOL care of patients with glioblastoma is the timing of the intervention. Among patients admitted to the hospital with advanced cancer, early goals-ofcare discussion, defined as their first goals-of-care discussion within the first 2 days of admission, was negatively associated with admission to intensive care units.²⁸ Additionally, it was found to be independently correlated with a 79% decrease in the likelihood of an inadvertent readmission to the hospital within a 90-day period.²⁸ Fifty-six percent of patients with glioblastoma lost functional independence 10 months after surgery,²⁹ and showed decreased medical decision-making ability compared to controls shortly after cancer diagnosis.⁶ Therefore, early intervention in patients with glioblastoma is very critical. The EANO Palliative Care Guidelines recommend early palliative care interventions and ACP at all disease stages, alongside standard referrals to palliative care services, at least at the time of tumor recurrence.^{3,4} The EANO guidelines also cited the timing of ACP as one of the areas of palliative care that deserves attention for future research, along with fatigue, disorders of behavior and mood, and supports for caregivers' needs. In 2021, The Improving Goal Concordant Care Initiative emphasized the need for action to guarantee that every patient with cancer and their families are provided with care that reflects their individual values and priorities. Additionally, it stressed the importance of primary oncology teams initiating and maintaining timely discussions with patients regarding their care goals.³⁰ However, discussions regarding care goals with patients diagnosed with advanced cancers typically commence at a later stage than optimal.

Further, research focusing on the introduction of early palliative care is lacking, and there have been no randomized controlled trials conducted in patients with glioblastoma thus far.³¹ In this study, palliative care consultation was able to reduce aggressive EOL care, even though it occurred at a very late stage, with a median time of 44 days from consultation to death, suggesting that palliative care consultation is critical for the EOL care of patients with glioblastoma. Therefore, further prospective studies are warranted and currently underway. The "Effect of early palliative care for patients with glioblastoma (EPCOG)" study represents one such effort, employing a randomized phase III clinical trial protocol to assess the impact of early palliative care interventions.³² Additionally, the development of a disease-specific ACP program underscores the recognition of the unique needs and challenges faced by patients with glioblastoma, prompting the exploration of tailored approaches to enhance their quality of care and support.³³ These initiatives collectively contribute to the growing body of research aimed at advancing our understanding of glioblastoma management and improving patient outcomes.

An interesting finding of our study was that patients who were religious were less inclined to undergo aggressive EOL care. Contrary to our findings, previous studies have reported that religion is associated with more aggressive EOL care. According to Phelps et al,³⁴ patients with advanced cancer who used religious coping were more likely to undergo intensive life-prolonging treatments nearing the end of life. People with religious beliefs were less likely to fill out a Do-Not-Resuscitate form, complete an AD, and receive ventilator and intensive life-prolonging treatments in the last week of life. A recent systematic review also reported that religiosity/spirituality/religious-spiritual coping is associated with more aggressive EOL treatments, as well as lower ACP rates in patients with cancer.35 The difference in the results may be due to ethnic, cultural, and religious differences, as previous studies have focused on White Christians, whereas this study focused on Koreans, 33% of whom followed a non-Christian religion. However, it is worth noting that only 13% of the patients filled out their own ADs, and the rest either did not have one, or had a family member fill one out for them. This makes the results difficult to interpret, and while additional information on family religion or the outcome of in-depth interview would have been helpful, the limitations of a retrospective cohort study made it difficult to obtain additional data.

The limitations of this study include that it was conducted retrospectively in a single Korean medical center and may have lacked generalizability, lack of data on symptoms, QoL, and caregiver satisfaction of individuals with end-stage cancer, and insufficient data on patients who were lost to follow-up. However, the National Agency for Management of Life-Sustaining Treatment oversees the uploading of all legal forms onto the Life-Sustaining Treatment Information Processing System, accessible at https://intra.lst.go.kr/login/ pkiLogin.do. Hospice nurses from registered medical institutions have gone through a certification process to verify whether a patient used a hospice organization and the date of death, allowing patients who were at loss to follow-up to obtain reliable information on hospice use and death.

Conclusion

The provision of palliative care consultation was significantly associated with the use of hospice care and reduced aggressive EOL interventions. To ensure better EOL care, physicians should promptly introduce ACP conversations and palliative care consultations for these patients early in the course of their disease. Prospective studies are needed to apply early palliative care counseling to patients with glioblastoma to increase self-determination, quality EOL care, and caregiver satisfaction.

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Conflicts of interest

The authors have no disclosures.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary material

Supplementary material is available at The Oncologist online.

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