

Causes of Death and End-of-Life Care in Patients With Intracranial High-Grade Gliomas

A Retrospective Observational Study

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Abstract

Background and Objectives

To understand patterns of care and circumstances surrounding end of life in patients with intracranial gliomas.

Methods

We retrospectively analyzed end-of-life circumstances in patients with intracranial high-grade gliomas at Columbia University Irving Medical Center who died from January 2014 to February 2019, including cause of death, location of death, and implementation of comfort measures and resuscitative efforts.

Results

There were 152 patients (95 men, 57 women; median age at death 61.5 years, range 24–87 years) who died from January 2014 to February 2019 with adequate data surrounding end-of-life circumstances. Clinical tumor progression ($n = 117, 77.0\%$) was the most common cause of death, with all patients transitioned to comfort measures. Other causes included, but were not limited to, infection (19, 12.5%); intratumoral hemorrhage (5, 3.3%); seizures (8, 5.3%); cerebral edema (4, 2.6%); pulmonary embolism (4, 2.6%); autonomic failure (2, 1.3%); and hemorrhagic shock (2, 1.3%). Multiple mortal events were identified in 10 (8.5%). Seventy-three patients (48.0%) died at home with hospice. Other locations were inpatient hospice (40, 26.3%); acute care hospital (34, 22.4%), including 27 (17.8%) with and 7 (4.6%) without comfort measures; skilled nursing facility (4, 3.3%), including 3 (2.0%) with and 1 (0.7%) without comfort measures; or religious facility (1, 0.7%) with comfort measures. Acute cardiac or pulmonary resuscitation was performed in 20 patients (13.2%).

Discussion

Clinical tumor progression was the most common (77.0%) cause of death, followed by infection (12.5%). Hospice or comfort measures were ultimately implemented in 94.7% of patients, although resuscitation was performed in 13.2%. Improved understanding of circumstances surrounding death, frequency of use of hospice services, and frequency of resuscitative efforts in patients with gliomas may allow physicians to more accurately discuss end-of-life expectations with patients and caregivers, facilitating informed care planning.

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Glossary

DNR/DNI = do not resuscitate/do not intubate.

Glioblastoma is the most common type of primary brain tumor in adults and is nearly universally fatal despite advances in therapy.^{1,2} However, cause of death from glioblastoma and other high-grade gliomas depends on many factors,³ including comorbid conditions, and clinical events surrounding death are frequently complex. Palliative care improves symptoms and quality of life in patients with cancer, particularly when engaged early in the disease process.⁴⁻⁸ The types of symptoms (e.g., cognitive impairment, seizures, difficulty ambulating) that patients with gliomas experience as the disease becomes refractory to treatment can affect quality of life and functional independence and may lead to hospitalization.⁹⁻¹⁵ Accordingly, patients with gliomas and their caregivers have specific palliative care and psychosocial needs.¹⁶⁻²² The frequency and settings in which palliative care and hospice services are used vary greatly.²³⁻²⁸ Uncertainty surrounding end-of-life expectations, including whether death involves physical pain or suffering, may exacerbate anxiety among patients and caregivers, who often ask about end-of-life circumstances in the setting of disease progression. Therefore, we sought to characterize cause and location of death as well as frequency of use of palliative measures and resuscitative efforts among patients with gliomas at a single academic medical center in a systematic and comprehensive manner over a 5-year period.

Methods

We conducted a single-institution retrospective study of adults with intracranial high-grade gliomas. In more detail, the Herbert Irving Comprehensive Neurologic Cancer Center Database (principal investigator, F.M.I.) is an institutional research database that is manually and prospectively annotated with clinical details extracted from the medical record of patients followed at Columbia University Irving Medical Center for neuro-oncologic care (by A.E.J.-G.). Demographics, date of diagnosis, and date of death are routinely collected in all available cases (by A.E.J.-G.). This database was manually reviewed (by A.E.J.-G.) to identify cases fulfilling the following inclusion criteria: (1) diagnosis of intracranial high-grade glioma, (2) age at diagnosis of at least 18 years, and (3) date of death from January 2014 to February 2019. We (M.B.) also screened patients who were alive when the study was initiated in December 2017 for inclusion on death until February 2019. For additional details pertinent to the current research study, the medical record was manually reviewed retrospectively (by M.B.) to determine and collect circumstances surrounding death, specifically (1) cause of death, (2) location of death, (3) performance of resuscitation, and (4) implementation of hospice or other comfort measures. Caregivers were surveyed if necessary to supplement the information available in the medical record. Cases without available details regarding circumstances surrounding death (1–4 above) were excluded.

Cause of death was defined as the primary clinical circumstance(s) immediately preceding and contributing to death for all patients. Death was attributed to tumor progression in cases of neurologic decline attributable to tumor growth with or without corresponding imaging. Location was categorized as home, inpatient hospice facility, acute care hospital, skilled nursing facility, or religious facility. Implementation of hospice services or other comfort measures, resuscitation status before death, and whether cardiac or pulmonary resuscitation were performed at the end of life, in addition to other relevant clinical variables, were also recorded. We defined comfort measures as supportive medical care for the purpose of controlling end-of-life symptoms, including comfort measures through formal hospice programs and other non-hospice-based comfort measures.

We defined cardiac resuscitation as use of basic life support or advanced cardiac life support protocols in an effort to restore spontaneous circulation after cardiac arrest. We defined pulmonary resuscitation as endotracheal intubation. Descriptive statistics were used for analyses.

Standard Protocols, Approvals, Registrations, and Patient Consents

We received approval from the Human Research Protection Office and Institutional Review Board of Columbia University to conduct this study, to retrospectively review medical records, and to survey caregivers as needed after obtaining verbal informed consent.

Data Availability

Requests should be submitted to the corresponding author.

Results

Study Population

There were 213 patients identified with intracranial high-grade gliomas who died during the 5-year interval of study. In 61, data regarding end-of-life circumstances (cause of death, location of death, performance of resuscitation, or implementation of hospice or other comfort measures) were unavailable in the medical record or from caregivers. Therefore, 152 patients (95 men, 57 women) made up the study cohort, for whom median age at death was 61.5 years (range 24–87 years, Table 1); histology was glioblastoma in 145 (95.4%, Table 2).

Cause of Death

Clinical tumor progression was the cause of death in most patients ($n = 177$, 77.0%; Table 3). These patients were transitioned to formal hospice programs or other non-hospice-based comfort measures in the setting of neurologic decline. Fatal infection occurred in 19 (12.5%), most commonly pneumonia ($n = 12$, 7.9%), which occurred in the

Table 1 Demographics (N = 152)

	No.	%
Sex		
Male	95	62.5
Female	57	37.5
Race		
White	124	81.6
Black or African American	3	2.0
Asian	6	3.9
Native Hawaiian or other Pacific Islander	1	0.7
Unknown	18	11.8
Ethnicity		
Hispanic or Latino	13	8.6
Non-Hispanic or Latino	126	82.9
Unknown	13	8.6
Preferred language		
English	140	92.1
Spanish	9	5.9
Italian	1	0.7
Hebrew	1	0.7
Russian	1	0.7
Level of education		
Less than high school graduate	8	5.3
High school graduate	30	19.7
College graduate	26	17.1
More than college graduate	40	26.3
Unknown	48	31.6
Age at death, y		
Median	61.5	
Range	21–87	

setting of aspiration in 8 (5.3%); 1 patient (0.7%) died of *Pneumocystis jiroveci* pneumonia. Five patients (3.3%) had intratumoral hemorrhage as a cause of death, 4 of whom were receiving therapeutic anticoagulation. Other infrequent mortal events are shown in Table 3. Multiple mortal events were identified in 10 (6.5%).

Location of Death

Nearly all patients (n = 144, 94.7%) died with hospice or other nonhospice comfort measures in place (Table 4). Most died at home (n = 73, 48.0%) or in an inpatient hospice facility (n = 40, 26.3%; Table 4). However, 34 (22.4%) died in an acute care hospital, 27 (17.8%) with comfort measures.

Table 2 Diagnosis (N = 152)

Histology	No.	%
Glioblastoma	145	94.8
Anaplastic astrocytoma	4	2.6
Anaplastic oligodendroglioma	2	1.3
High-grade glioma (not further specified)	1	0.7

Resuscitation

Most patients (n = 132, 86.8%) did not undergo cardiac or pulmonary resuscitation (Table 5). Pulmonary resuscitation (without cardiac resuscitation) occurred in 15 patients (9.9%), 12 (7.9% overall) of whom were ultimately transitioned to hospice or other comfort measures before death, but the remainder (n = 3, 2.0% overall) died in acute care hospitals. One patient (0.7%) was intubated early in the disease course for unresponsiveness but was successfully extubated and received tumor-directed therapy; when clinical tumor progression occurred, a “do not resuscitate/do not intubate” (DNR/DNI) order was entered, and the patient died on home hospice. Five patients (3.3%) remained intubated and mechanically ventilated at the time of death.

No order was obtained to avoid resuscitation for 1 patient (0.7%), resulting in suctioning and bag-mask ventilation at the end of life; caregivers ultimately refused intubation and chest compressions at the time of cardiopulmonary arrest. Unsuccessful cardiac resuscitation without intubation was performed in 1 (0.7%, Table 5).

Reasons for resuscitation varied. For example, cardiac or pulmonary resuscitation was performed in 6 patients (3.9%) because of religious concerns. Hope for longer survival to receive an additional therapy prompted resuscitation in 3 patients (2.0%). Rapid and unanticipated decline early in the disease course drove resuscitation in 4 patients (2.6%).

Only 68 patients (44.7%) had clear DNR/DNI documentation present in the medical record. In 18 (11.8%) other cases, caregivers clarified that DNR/DNI documentation was completed.

We identified 4 patients who died 1 to 3 months after diagnosis. Among them, 3 had comfort or hospice measures implemented. Tumor progression, respiratory failure, pneumonia, and malignant cerebral edema were the cause of death in 1 patient each. Resuscitation was performed in 3 (pulmonary in 2, cardiac in 1). The small sample size precluded formal statistical comparisons against other subgroups with longer survival.

Discussion

In our clinical experience, patients and caregivers often ask what to expect over the arc of the illness as gliomas worsen. We found that most (77.0%) died of (presumptive) tumor

Table 3 Cause of Death

Cause ^a	No.	%
Clinical tumor progression	117	77.0
Intratumoral hemorrhage	5	3.3
Seizures	8	5.3
Cerebral edema	4	2.6
Infection	19	12.5
Pneumonia	12	7.9
<i>Pneumocystis jiroveci</i> pneumonia	1	0.7
Other	11	7.2
Urinary tract	5	3.3
CNS ^b	4	2.6
Progressive multifocal leukoencephalopathy	1	0.7
Ventriculitis/meningitis	2	1.3
Multiorgan bacteremia and sepsis	1	0.7
Gastrointestinal	2	1.3
Pulmonary embolism	4	2.6
Hemorrhagic shock	2	1.3
Autonomic failure	2	1.3
Secondary to adrenal insufficiency	1	0.7
Unknown cause	1	0.7
Respiratory insufficiency, unknown cause	2	1.3
Pulmonary edema	1	0.7
Cardiac arrhythmia	1	0.7

^a Total exceeds 100% because 10 patients had >1 fatal comorbidity and 3 had >1 source of infection.

^b None perioperative.

growth and that transition to hospice or other non-hospice-based comfort measures in the setting of resultant neurologic decline was possible. For example, nearly all patients (94.7%) died with hospice or other comfort measures in place, and 74.3% died either at home or as part of an inpatient hospice program. Only 13% underwent cardiac or pulmonary resuscitation. These observations suggest that death was natural and comfortable, but we did not formally assess levels of pain, symptom distress, or psycho-existential distress. We are unaware of similar studies.

Specific neurologic complications of tumor progression such as refractory seizures, painful intratumoral hemorrhage, and symptomatic cerebral edema were identified as infrequent clinical events leading to death compared with clinical tumor progression. Seizures are a known complication of gliomas, particularly during the last week to month of life, and often affect quality of life.^{10,12,14} Only 5.3% of patients in this study,

Table 4 Location of Death (N = 152)

Location	No.	%
Home with hospice	73	48.0
Inpatient hospice	40	26.3
Acute care hospital	34	22.4
With comfort measures	27	17.8
Without comfort measures	7	4.6
Skilled nursing facility	4	2.6
With comfort measures	3	2.0
Without comfort measures	1	0.7
Religious facility	1	0.7
With comfort measures	1	0.7
Without comfort measures	0	0

however, had seizures at the end of life, perhaps due to adequate counseling for caregivers about seizure risk and aggressively treating epilepsy.

Approximately one-half (48.0%) of our patients died at home. Location of death is often very important to patients with cancer, including primary brain tumors. Dying in the preferred place of death improves quality of care.^{29,30} Patients often prefer to die at home; however, late hospitalization—at times including intensive care—and death in an acute care hospital occur commonly in patients with both systemic malignancies and primary brain tumors.^{29,31-34} In-hospital death, including death in the intensive care unit, is associated with poorer quality of death in patients with cancer and

Table 5 Resuscitation (N = 152)

Resuscitation	No.	Percent
None	132	86.8
Hospice or other comfort measures	131	86.2
No hospice or other comfort measures	1	0.7
Pulmonary (without cardiac)	15	9.9
Hospice or other comfort measures	12	7.9
No hospice or other comfort measures	3	2.0
Cardiac (without pulmonary)	1	0.7
Hospice or other comfort measures	0	0
No hospice or other comfort measures	1	0.7
Cardiac and pulmonary	4	2.6
Hospice or other comfort measures	1	0.7
No hospice or other comfort measures	3	2.0

increased risk of psychological distress among caregivers.³⁵ Patients with gliomas who receive palliative care are more likely to die outside the hospital setting, particularly if enrolled in hospice >7 days before death.³⁶ In our study population, nearly one-fourth (22.4%) died in an acute care hospital. Further efforts to engage palliative services at home to reduce the need for inpatient support are warranted to improve both quality and cost-effectiveness of care at the end of life in patients with brain tumors.^{20,37}

Although 86.8% of patients did not undergo acute cardiac or pulmonary resuscitation, only 45% had clear documentation of a DNR/DNI preference in the medical record, consistent with the literature suggesting that advanced directives are often poorly documented in patients with gliomas.^{29,34}

More robust efforts to discuss and document resuscitation status in patients with gliomas are needed to increase preparedness for the end of life. In 3.9% of patients in our cohort, resuscitative efforts were requested by caregivers for religious reasons. Religious concerns in patients with cancer, including glioblastoma, can be associated with increased risk for late hospitalization and receipt of futile medical care near the time of death,^{33,38} even though patients with advanced cancer may perceive that their spiritual needs are not supported.³⁹ Further investigation is warranted regarding care patterns in religiously observant patients and the required specific support.

There are several limitations to our study. As a result of the retrospective nature of the study, we were limited to extracting data from the clinical record as opposed to prospectively collecting prespecified points in a uniform manner. We ameliorated this by contacting caregivers, but recall bias could have influenced the supplemental information provided. Furthermore, while 213 patients with high-grade gliomas who died within the 5-year time frame of the study were identified, 61 were excluded due to insufficient available information from the medical record or caregivers regarding end-of-life circumstances. Thus, selection bias may have affected our observations of end-of-life outcomes, because only those patients who had adequate end-of-life data in the medical record or whose caregivers were able to provide supplemental information when needed were included. In addition, as a single-center study at a major urban academic center, our results may not be generalizable to other settings. Finally, we did not formally compare end-of-life circumstances by duration of survival.

Improved understanding of the most common clinical circumstances surrounding death and the frequency of hospice use, comfort care, and resuscitative efforts in patients with gliomas nearing death may ultimately allow physicians to provide more accurate expectations and options for end-of-life care, thus reducing anxiety and uncertainty about the end of life and permitting more thorough, informed care planning. Our observation that nearly all patients (94.7%) died with hospice or other comfort measures suggests that a peaceful

death from glioma is possible; however, we did not formally measure comfort or pain. Because use of chemotherapy in the last months of life is associated with increased use of aggressive measures such as mechanical ventilation and cardiopulmonary resuscitation in patients with systemic malignancies,⁴⁰ the field of neuro-oncology would also benefit from analyzing how circumstances surrounding death, including comfort, hospitalization, and resuscitation, are affected by continuation of aggressive disease-modifying therapy (such as surgery, radiotherapy, or chemotherapy) in the last months of life for patients with gliomas.

In conclusion, clinical tumor progression was the most common cause of death in our patient population, and most patients died at home with hospice or in an inpatient hospice facility. The majority of patients were placed on hospice or non-hospice-based comfort measures and were not resuscitated at the end of life. These results may inform end-of-life expectations by patients and caregivers, fostering care planning and emotional preparedness.

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Disclosure

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Appendix (continued)

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