# CNS Oncology

# Primary brain tumor patients admitted to a US intensive care unit: a descriptive analysis

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**Purpose:** To describe our population of primary brain tumor (PBT) patients, a subgroup of cancer patients whose intensive care unit (ICU) outcomes are understudied. **Methods:** Retrospective analysis of PBT patients admitted to an ICU between 2013 to 2018 for an unplanned need. Using descriptive analyses, we characterized our population and their outcomes. **Results:** Fifty-nine PBT patients were analyzed. ICU mortality was 19% (11/59). The most common indication for admission was seizures (n = 16, 27%). **Conclusion:** Our ICU mortality of PBT patients was comparable to other solid tumor patients and the general ICU population and better than patients with hematological malignancies. Further study of a larger population would inform guidelines for triaging PBT patients who would most benefit from ICU-level care.

**Lay abstract: Purpose:** Data are lacking regarding outcomes of patients with primary brain tumors (PBTs) admitted to an intensive care unit (ICU), which may it difficult for ICU providers to know who of these patients will best benefit from ICU-level care. We aimed to describe our patient population to contribute to the limited data. **Methods:** We performed a retrospective analysis of critically ill PBT patients in our ICU. **Results:** Of 59 patients analyzed, ICU mortality was 19% (11/59), and the most common indication for admission was seizures (n = 16, 27%). **Conclusion:** Our ICU mortality of PBT patients was comparable to other solid tumor patients and the general ICU population and better than patients with hematological malignancies.

Intensive care unit (ICU) resources are limited and expensive, and intensivists are often faced with decisions regarding which patients will be allocated ICU-level care. It is difficult to assess who will most benefit from an ICU stay based on clinical judgment alone. Data show that cancer diagnoses are viewed as unfavorable risk factors for an admitting ICU physician [1], and metastatic cancer has been associated with ICU refusal [2]. However, it has been shown that intensivists who use their clinical judgment to triage cancer patients for ICU admission are inaccurate one-quarter of the time [3].

Despite a fair amount of research on the outcomes of patients with solid tumors and hematological malignancies admitted to an ICU, there is a lack of data regarding primary brain tumor (PBT) patients [4]. PBT patients are a unique group of oncological patients, with heterogeneity within this group based on patient age and tumor type [5]. Yet studies often do not separate patients with PBTs from other solid or hematological malignancies. Whether it is reasonable to lump PBT patients in with patients with solid tumors has not been well investigated. On the basis

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of current data, the impact of the diagnosis, admission reason or tumor control status of PBT patients on ICU outcomes is not clear.

Only two studies, based in French ICUs, have evaluated this topic of PBT patients admitted to an ICU for an acute ICU need [6,7]. They report ICU mortality outcomes (22–23%) [6,7] that are comparable to patients with solid tumors (17–23%) [4,8] and within the range of a general ICU patient without a cancer diagnosis (3–67%) [9–12]. Between the two studies, an admission diagnosis of seizures was associated with a favorable outcome, but there were differing conclusions about whether tumor control status was a predictor of outcome (one study concluded not) [6,7]. The combined sample size of the studies was 267 patients, reflecting the rarity of the disease and the need for additional studies to supplement their data [6,7].

To address this need, we aimed to characterize PBT patients admitted to our institution's ICUs. We sought to describe these patients, their admission reasons and their outcomes. To the best of our knowledge, this is the first study to evaluate this specific population in the US.

## Methods

We performed a single-institution retrospective analysis of PBT patients with an established outpatient neurooncologist, who experienced an unplanned admission to a Duke Health System (DHS) ICU between 1 July 2013 and 12 April 2018.

### Patient care sites

The Preston Robert Tisch Brain Tumor Center (PRTBTC) provides comprehensive oncological care for brain tumor patients. The center sees up to 900 new adult PBT patients and up to 75 new pediatric PBT patients annually. The PRBTC has an interdisciplinary model that includes specialists in neurooncology, neurology, radiation oncology and neurosurgery. In addition to outpatient clinic visits for follow-up and treatments, patients are also followed by the neurooncology staff on a dedicated inpatient medical neurooncology service and in the ICU. While in the ICU, patients are managed by a multidisciplinary provider team from neurocritical care, neurosurgery, neurology and neurooncology.

The DHS comprises multiple ICUs across three hospitals located in the Durham-Raleigh, North Carolina, area, with the majority of the neurooncology patients being seen in a dedicated neuro-ICU.

### Clinical databases

The DukE Neurocritical Care Patient Data Repository (DENDRITe) is an electronic database comprising patients admitted to a DHS ICU with patient demographic and admission data collected from DHS electronic medical record (Epic/Maestro Care). The PRoGREss registry (Pro00027120) is a retrospective and prospective chart review study of all patients diagnosed after 31 December 2004 with a primary CNS tumor who were seen at the PRTBTC and consented for research participation. Additional information outside of these databases was obtained via chart reviews from the DHS electronic medical record.

### Patient population

Using the DENDRITe and PRoGREss patient registries, we retrospectively identified adult patients over 18 years old admitted to a DHS ICU between 1 July 2013 to 12 April 2018 with a histologically confirmed PBT. DENDRITe was initially searched for patients admitted to a DHS ICU during the research time period with 'glioma' or 'brain tumor' in their history or diagnosis code. Additional Current Procedural Terminology codes searched included those for the following diagnoses: meningioma (C70.9, D32.0, D42.0, D42.9, Z86.011, Z86.018, Z98.890), primary CNS lymphoma (C85.89) and malignant neoplasm of the brain (C71.7, C71.8, C71.9, Z85.841). The medical record numbers of the DENDRITe list generated was cross-matched with those patients consented by their primary neurooncologists for the PRoGREss registry.

We included patients with an unplanned ICU admission. 'Unplanned admission' relates to patients who were not admitted for routine postoperative monitoring after an elective resection of a tumor or for a research protocol that required ICU-level monitoring. We only included the first admission for patients with multiple ICU admissions.

### Data collection

To describe the current practice, we extracted the following data of each patient's admission from the DENDRITe database and via chart reviews of the electronic medical record: demographics, presence of co-morbidities at time

of admission, tumor characteristics, extent of prior tumor resection, disease status, palliative care consult during admission, reason(s) for admission, time of symptom onset to ICU admission, and code status before discharge.

Tumor characteristics included histologic diagnosis, histologic grade, disease site category (frontal lobe, parietal lobe, temporal lobe, multiple, other), extent of resection, and current disease status (new diagnosis, stable, or active recurrence). Histologic diagnosis and grade were defined by the 2016 WHO Classification of Tumors of the Central Nervous System [13].

Reasons for admission were categorized as either Neurosurgical, Neurological or Systemic. Neurosurgical indications for admission involved problems directly related to a previous neurosurgical intervention. Specific examples include shunt malfunction or infection, postoperative wound infection and postoperative cerebrospinal fluid leak. Neurological indications involved issues related directly to the CNS, not related to a prior neurosurgical intervention. Specific examples include seizures, CNS infection not related to a neurosurgical device or procedure, hydrocephalus, hemorrhagic stroke, ischemic stroke and disease recurrence. Status epilepticus was defined as greater than or equal to 5 min of continuous seizure or two or more discrete seizures between which there is incomplete recovery of consciousness, as defined by the International League of Epilepsy and Neurocritical Care Society [14,15]. Systemic indications included problems related to all other organ systems.

We documented the presence of organ failure during the ICU stay: respiratory failure requiring invasive mechanical ventilation, hemodynamic instability requiring vasopressor support and/or renal support requiring continuous or renal replacement therapy. Multiorgan failure was defined as the presence of two or more organ failures. None of our patients experienced a cardiac arrest or liver failure; thus, these categories of organ failure were not included in our analyses. We also documented the presence of a poor Glasgow Coma Scale (GCS) on admission (defined as GCS = 3) [16].

APACHE II and SAPS II scores are severity indices validated in the ICU communities [17,18], and the Charlson Comorbidity Index (CCI) is validated in the cancer community as an indicator of long-term mortality [19]. These measures were calculated based on information extracted from the patient's admission history and physical and laboratory data available at the time of the patient's admission to the ICU as markers of the patient's severity of disease upon admission.

Outcomes described included ICU and hospital mortality rates; ICU and hospital length of stay; median overall survival; 30-, 60- and 90-day survival; and discharge disposition (home with self-care, home with home health, acute rehabilitation facility, skilled nursing facility, long-term acute care, home hospice, hospital medical inpatient and expired). The patient's performance status before and after admission, when applicable, were determined by the Karnofsky Performance Status (KPS) scale documented in the outpatient neurooncology notes [20]. We collected each patient's KPS before admission and at 2, 4 and 6 months postdischarge [20].

## Statistical analysis

Due to the small sample size, the majority of the analyses in this article are descriptive. Categorical variables were described using frequencies and percentages, and continuous variables were summarized using either means and standard deviations (SDs) or medians and interquartile ranges (IQRs) where appropriate. To estimate overall survival of our study cohort, Kaplan–Meier methods were used. Overall survival was defined as the number of months between the date of admittance to ICU and death, and subjects were censored at the date of last contact if they remained alive. SAS Version 9.4 was used to generate descriptive statistics and survival calculations for this analysis. For the visualizations in Figures 1 & 2, we used R version 3.6.1 and the ggplot2 package.

## Ethics

All patients were consented for research participation, and the Duke Institutional Review Board approved this study.

## Results

Between 1 July 2013 and 12 April 2018, there were 305 admissions to the ICU of PBT patients followed by the PRTBTC. Following the exclusion of 207 admissions that were routine postoperative admissions to the ICU, 36 for research study and three repeat admissions, we analyzed the data of 59 patients who experienced unplanned admissions.

Median age was 54 (IQR: 43–64), and 36 patients (61%) were male (Table 1). Twenty-six patients (44%) had
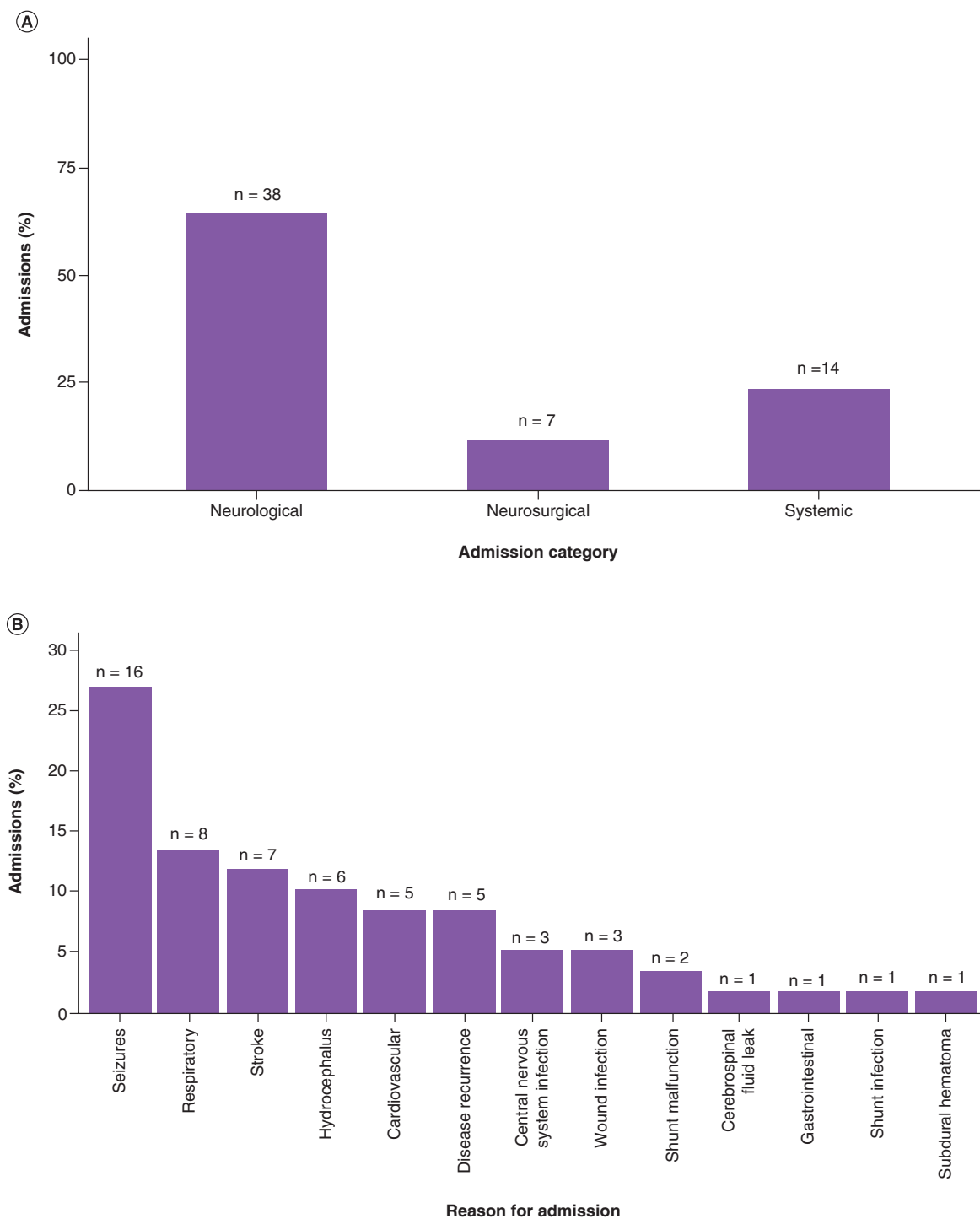
**(A)**



**(B)**



**Figure 1.    Admission indications. (A)** Admission indication by category. **(B)** Admission indication by specific reason.

no comorbidities (Table 1). The mean GCS on admit was 11 (SD = 4.4, range: 3–15). The mean time of symptom onset to admission to ICU was 4 days (SD = 7.4, range: 0–42 days).

The most common histologic diagnosis was high grade glioma (n = 35, 59%), and most patients had recurrent disease (n = 33, 56%) (Table 1).  Additional patient characteristics are noted in Supplementary Table 1.

Most patients were admitted for a neurological indication (n = 38, 64%, Figure 1A). The most common reasons for admission were seizures (n = 16, 27%), followed by respiratory failure (n = 8, 14%) and stroke (n = 7, 12%)
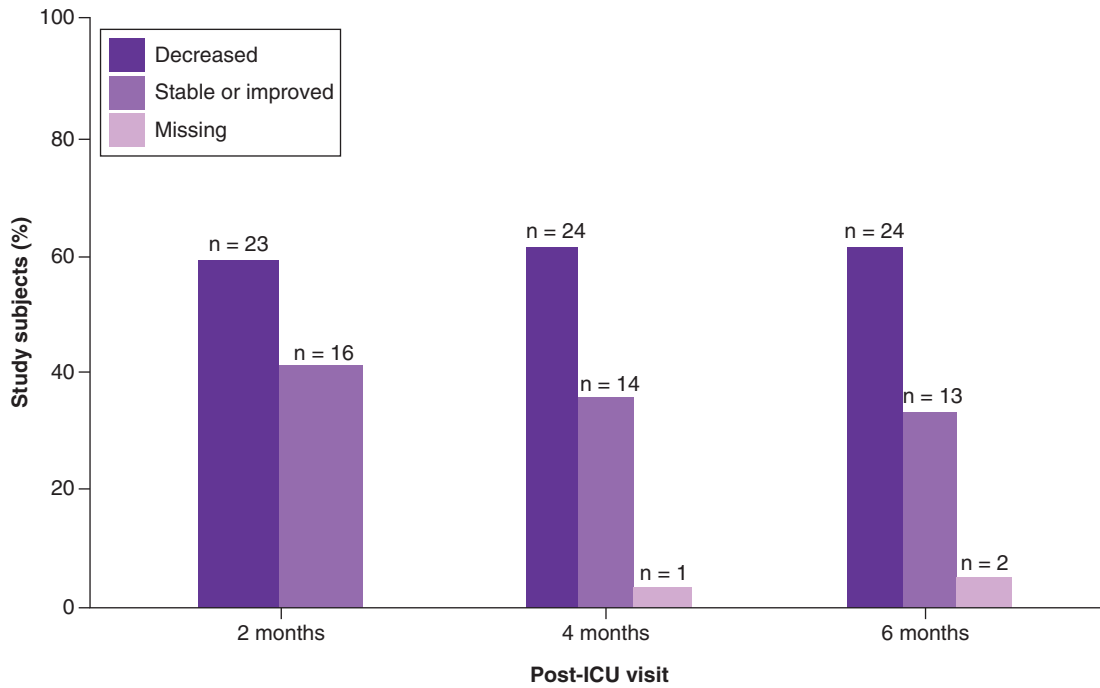
**Figure 2.**   **Functional outcomes of intensive care unit survivors based on Karnofsky Performance Scale.**
ICU: Intensive care unit; KPS: Karnofsky Performance Scale.

| Table 1. Demographics, admission and tumor characteristics of primary brain tumor patients admitted to the intensive care unit. | |
|---|---|
| **Characteristics** | **n = 59** |
| Age (year), median (IQR) | 54 (43–64) |
| Male gender, n (%) | 36 (61.0) |
| No comorbidities, n (%) | 26 (44.1) |
| Glasgow coma scale, mean (SD) | 11 (4.4) |
| Time of onset until admission to ICU (days), mean (SD) | 4 (7.4) |
| **Histologic diagnosis, n (%)** | |
| Low grade glioma | 15 (25.4) |
| High grade glioma | 35 (59.3) |
| Meningeal tumor | 6 (10.2) |
| Primary CNS lymphoma | 2 (3.4) |
| Other[†] | 1 (1.7) |
| **Disease status, n (%)** | |
| Newly diagnosed | 13 (22.0) |
| Stable disease | 13 (22.0) |
| Recurrent disease | 33 (55.9) |
| [†]Medulloblastoma. | |
| ICU: Intensive care unit; IQR: Interquartile range; SD: Standard deviation. | |

(Figure 1B). Among the 16 patients admitted for seizures, nine (56%) were admitted for status epilepticus. Among the seven patients admitted for stroke, six (86%) were admitted for intracranial hemorrhage.

    Twenty-eight patients (47%) suffered some form of organ failure: 24 required mechanical ventilation (41%), one required renal replacement therapy (2%), six required the use of vasopressors (10%) and three patients (5%) suffered two organ failures (mechanical ventilation and use of vasopressors) (Table 2).

| Table 2. Complications, severity, outcomes and disposition of primary brain tumor patients admitted to the intensive care unit. | |
|---|---|
| **Characteristics** | **n = 59** |
| **Presence of organ failure, n (%)** | |
| Mechanical ventilation | 24 (40.7) |
| Renal replacement therapy | 1 (1.7) |
| Use of vasopressors | 6 (10.2) |
| Two or more organ failures | 3 (5.1) |
| Total patients | 28 (47.5) |
| **Severity indices, median (IQR)** | |
| APACHE II | 12 (7–18) |
| SAPS II | 30 (22–44) |
| Charlson Comorbidity Index | 2 (2–3) |
| Charlson Comorbidity Index (excluding tumor diagnosis) | 0 (0–1) |
| **Outcome** | |
| ICU mortality, n (%) | 11 (18.6) |
| Hospital mortality, n (%) | 12 (20.3) |
| Length of stay in ICU (days), mean (SD) | 7 (6.0) |
| Length of stay in hospital (days), mean (SD) | 11 (8.1) |
| Median survival (months), median (95% CI) | 6 (1.1–15.5) |
| 3-month survival, % (95% CI) | 58 (44.1–69.0) |
| 6-month survival, % (95% CI) | 49 (35.7–61.0) |
| 12-month survival, % (95% CI) | 44 (30.9–55.9) |
| 24-month survival, % (95% CI) | 32 (19.9–44.1) |
| **Discharge disposition, n(%)** | |
| Home | 24 (40.7) |
| – Self-care | 14 (23.7) |
| – Home health service | 10 (17.0) |
| Acute rehabilitation facility | 5 (8.5) |
| Skilled nursing facility | 9 (15.3) |
| Long-term acute care | 1 (1.7) |
| Hospice | 8 (13.6) |
| Died | 12 (20.3) |
| ICU: Intensive care unit; IQR: Interquartile range; SD: Standard deviation. | |

Severity indices on admission were calculated. The median APACHE II score was 12 (IQR: 7–18), SAPS II was 30 (IQR: 22–44) and CCI was 2 (IQR: 2–3) (Table 2).

The ICU mortality rate was 19% (11/59). One patient was transferred out of the ICU on comfort care and died in an acute care bed; thus, the hospital mortality rate was 20% (12/59) (Table 2). The mean ICU length of stay was 7 days (SD = 6 days). The mean inpatient length of stay was 11 days (SD = 8 days). Twenty-four patients (41%) were discharged home, with 14 of these patients able to perform self-care. Eight were discharged to hospice (14%) (Table 2). Of note, the majority of patients admitted for seizures survived (14/16, 88%); only two died in the ICU after transitioning to comfort care.

Of the 39 ICU survivors (not discharged to hospice or who died during their admission), the KPS before admission was compared with the KPS at the 2-, 4- and 6-month follow-up visits postdischarge. Overtime, the KPS decreased for the majority of patients (Figure 2). However, the majority of patients (n = 29, 74%) were functioning at a KPS at or greater than 70 (able to perform self-care) before admission, reflecting a high baseline, and almost half (n = 19, 49%) of patients had a stable or improved KPS at some point after their ICU admission (Supplementary Figure 1).

## Discussion

This is the first descriptive analysis in the US evaluating PBT patients with an unplanned admission to an ICU. Our ICU mortality rate of 19% was similar to two similar French studies of PBT patients (22–23%) [6,7], similar to patients with solid tumors (17–23%) [4,8], better than patients with hematologic malignancies (40–46%) [4,21,22] and within the range expected for general ICU patients (3.4–66.7%) [9–12]. In addition to similar ICU mortality, our most common reasons for admission were similar to the two prior studies conducted in France: seizures and respiratory failure [6,7].

Our study showed a survival rate of 88% in patients admitted for seizure, consistent with prior studies [6,7]. With only 12 hospital deaths within this small population, our ability to definitively assess predictors of survival is limited. Therefore, questions remain regarding outcome predictors of PBT patients and how they compare with patients with other cancers. One can hope to validate and explore potential predictors in a larger retrospective or prospective study.

In 39 patients for whom data were available, we compared the KPS before admission and up to 6 months post-ICU discharge. The majority of our patients (62%, 24/39) had a decreased KPS at 4 months postdischarge. This statistic was evaluated by Tabouret *et al.* in 35 patients, and they determined that the majority of their patients (77%, 27/35) had improved KPS at 4 months postdischarge [6]. The differences in the change of KPS between our studies are difficult to compare because the baseline of our population was at a high level of function and these data are not available in Tabouret's population. However, it is a relevant point to study because an important question regarding aggressive ICU care is not only mortality outcomes but also quality-of-life years gained from surviving the admission. Survival with an undesirable quality of life from a patient and family perspective postdischarge may have many implications regarding decisions made while in the inpatient setting, and is an area of potential future study.

Despite the small sample size, this study contributes to the dearth of research related to PBT patients admitted to an ICU for an acute need and their outcomes. The current data published have limited sample sizes (a total of 267 patients across three ICUs) [6,7]. The PBT population is crucial population to study further because the results will affect ICU triage decisions and aggressiveness of care for these patients with a presumptive terminal diagnosis. If a particular brain tumor pathology is associated with no impact on ICU mortality and the reasons for admission (i.e., seizure) are associated with a favorable outcome, then this should prompt intensivists to be optimistic in their ability to admit the patient and provide optimal care. Similarly, if tumor progression is associated with poor ICU outcome, then providers may suggest a time-limited trial for these patients in the ICU and early introduction of palliative care measures.

## Conclusion

This is the first descriptive analysis of a population of PBT patients admitted to an ICU for an acute need in the US. The ICU mortality was 19% (11/59), which is comparable to the ICU mortality for a general ICU patient and patients with solid tumors admitted to an ICU, and also corroborates data from two prior French studies. The primary reason for admission was seizure. PBT patients encompass a heterogeneous group of patients with variable prognoses, many of whom have no other comorbidities and suffer unique, treatable complications. Further validation of risk factors for ICU mortality should be studied in larger populations to guide decisions on triaging ICU admissions and the aggressiveness of care.

## Future perspective

Without additional data regarding predictors and outcomes of critically ill brain tumor patients, intensive care unit (ICU) providers can only assume which patients will most benefit from ICU level care. Further research may show that seizures, including status epilepticus, is an ICU admission indication that is treatable and will benefit from aggressive care in the ICU. On the other hand, admission indications related to disease progression that is inoperable may carry a worse ICU outcome. As predictors of ICU outcomes are further delineated, ICU providers will not only gain more confidence in how to best allocate limited ICU resources, they will be better able to conduct goals-of-care conversations with family along with the neurooncologists and neurosurgeons.

> ### Summary points
>
> - The mortality of critically ill primary brain tumor patients was similar to other general intensive care unit (ICU) patients, and the most common reason for admission was seizures.
> - Almost half of patients with long-term outcomes had a stable or improved Karnofsky Performance Status Scale within 6 months postdischarge.
> - Critically ill primary brain tumor patients are a unique subgroup of ICU patients that warrants further study regarding predictors of ICU outcomes to inform their benefit of ICU level care.

### Ethical conduct of research

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the IRB at each of the participating institutions listed on the title page.

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