Clinical Implications of Status Epilepticus in Patients With Neoplasms

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Objectives: To elucidate factors that contribute to the development of status epilepticus (SE) and determine prognostic factors and the impact on 30-day survival.

Design: Retrospective review of medical records.

Setting: University of Virginia Health System.

Patients: Thirty-five patients with SE secondary to a tumor, either primary or systemic, or its treatment.

Main Outcome Measures: Seizure control, 30-day mortality, and overall survival.

Results: Status epilepticus most commonly occurred at tumor presentation or progression and was controlled in all cases. Thirty-day mortality was 23%. Patients with systemic cancer were at higher risk of death, although they were older and had more acute comorbidities. Age, tumor type, status of tumor at time of event, history of epilepsy, and status type were not predictive of mortality. Age was associated with a higher rate of nursing home placement and shorter overall survival. Overall survival was determined by underlying tumor.

Conclusions: Status epilepticus in patients with cancer is responsive to therapy. Workup of underlying causes is indicated, even in the presence of subtherapeutic antiepileptic drug levels, because coexistent conditions contributing to the development of SE may be present. In those with known cancer, brain imaging should be performed because SE usually occurs in the setting of tumor progression or new metastases.

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Status epilepticus (SE) is a neurological emergency well studied within the general population. Despite a high incidence of seizures among patients with brain tumors, SE remains poorly understood in this population. Specifically, little is known of its responsiveness to therapy and impact on short-term and long-term outcome. We undertook this study to explore these issues by analyzing patient and tumor variables to identify prognostic factors.

METHODS

The Clinical Data Repository at the University of Virginia was queried for patients discharged with SE (International Classification of Diseases, Ninth Revision [ICD-9] code of 345.2, 345.3, 345.7, or 345.71) between January 1995 and December 2002. Discharge summaries of identified patients were reviewed and patients with cancer, identified. Patients were also identified within the University of Virginia Neuro-Oncology Clinic. Hospital, radiology, and pathology records were scrutinized and relevant data, abstracted. Primary brain tumor included neoplasms that arose primarily from within the brain parenchyma or the meninges. Patients with systemic cancers were included if SE was related to cerebral metastases or a complication of their treatment. Status epilepticus was defined as persistent seizure activity on arrival to the emergency department or seizure activity reliably documented as lasting 30 minutes. Status epilepticus was considered a complication if it occurred within 30 days of surgery or radiation or was secondary to a well-established adverse effect of treatment. Intractable SE was defined as the need for 3 or more medications to resolve seizure activity. If both lorazepam and diazepam were used, 4 or more medications were required for SE to be considered intractable. Progression was defined as radiographic changes consistent with tumor progression occurring within 30 days of the index event. Acute illnesses were significant systemic or central nervous system disorders occurring independently of the tumor that likely contributed to the development of SE. Mortality from SE was defined as death within 30 days of the event. The University of Virginia institutional review board approved this study. Statistical analysis methods included Kaplan-Meier univariate survival analyses.
RESULTS

Five hundred fifty-five patients were discharged with the queried ICD-9 codes. The query revealed 50 patients with a concurrent diagnosis of cancer, of whom 28 had SE related to either the tumor or its treatment. Seven additional patients fulfilling these criteria were identified within the Neuro-Oncology database. These 35 patients are the subject of this study.

Patient demographics and tumor histologic features are displayed in Table 1. Tumor status at the time of SE and antiepileptic drug (AED) use are presented in Table 2. Patient workup at presentation was heterogenous, although all patients underwent neuroimaging and a serological screen (comprehensive blood cell counts and chemistries) at presentation. Among patients with gliomas and metastatic lesions, only 15.6% developed SE in the presence of preexisting, stable disease. In contrast, 60% of patients with meningiomas had stable disease. Of patients with subtherapeutic AED levels, 2 had radiographic progression and 2 others had acute illnesses at the time of SE. Management of SE was heterogenous, although all patients underwent neuroimaging and phenytoin. Three patients were treated with phenobarbital, and 1 patient received propofol. Medically induced coma was required for 1 patient.

Characteristics of the 8 patients who died within 30 days of SE and survivors are presented in Table 3. There were no statistically significant differences in survival at 30 days between older and younger patients (P = .38), between the 4 seizure types (P = .22), whether patients had had prior seizures (P = .19), or whether patients had been intubated (P = .20). The impact of the tumor status at the time of SE (new diagnosis, progression, or stable disease) could not be statistically analyzed because only 1 patient from each group died within 30 days. Similarly, only 1 patient with intractable SE died. Obviously, there was no difference in survival between these groups. There was a significant difference (P = .01) in survival at 30 days attributable to tumor histologic features; 50% of patients with systemic cancer died within 30 days, whereas only 14% of patients with primary brain tumors died within 30 days.

In further analysis of the effect of age on length of survival, 5 patients (71%) older than 70 years and 15 patients (54%) younger than 70 years died at a median of 44 and 154 days, respectively (P = .049). Age also related to patient disposition after SE; 5 older patients (71%) were discharged to a nursing home, 4 of whom previously resided at home, whereas only 1 younger patient (4%) previously living at home was discharged to a nursing home.
Status epilepticus is poorly studied among patients with cancer. Yet patients with brain tumors are at risk of this potentially fatal condition, because they compose 4% to 12% of adults with SE.\textsuperscript{1,6} Although SE affects patients with central nervous system and systemic malignancies, it is more common among patients with primary brain tumors. Seizures in general are more common among patients with primary brain tumors, affecting 20% to 40% of patients at presentation and an additional 20% to 40% during the course of their illness.\textsuperscript{7} Comparatively, fewer than 20% of patients with central nervous system metastases present with seizures.\textsuperscript{8-10} with an additional 10% developing seizures during their illness.\textsuperscript{9,11}

Thirty-day mortality in our series was 23%, which is consistent with mortality from SE of all causes (15%-23%).\textsuperscript{1,3,6,12} It has been reported that SE secondary to tumor carries a higher rate of mortality (30%-40%) relative to other causes,\textsuperscript{3,6,13} although in this series mortality appears to be more related to what would be expected from natural disease progression. Overall survival correlated well with predicted survival from the underlying tumor. The median survival of our patients with glioblastoma multiforme and cerebral metastases was 12 and 5 months, respectively, from time of diagnosis of cerebral lesion, which closely approximates historical controls. On the contrary, 4 of 5 patients with meningioma remain alive. Thus, in this study, SE in patients with cancer does not appear to adversely impact long-term survival.

Gliomas accounted for the majority of primary brain tumors in this series. Because these tumors are the most common symptomatic primary brain tumors and are often associated with epilepsy, this is not unexpected. Low-grade gliomas and tumors with an oligodendrogial component each accounted for 35% of the gliomas, exceeding the relative incidence of these tumor types in the general population. These tumor types, however, are more epileptogenic compared with their high-grade and astrocytic counterparts.\textsuperscript{14,15}

Among patients with gliomas and central nervous system metastases, SE usually developed at the time of tumor progression or diagnosis. A similar pattern has been observed with seizures in patients with gliomas, in whom they often represent a disease-presenting symptom\textsuperscript{15,16} or occur at the time of tumor progression.\textsuperscript{11,16} In a retrospective review of 65 patients with gliomas and seizures (including 10 patients with SE), Moots et al\textsuperscript{16} noted that SE occurred at presentation in 2, with tumor progression in 4, and following biopsy and radiosurgery in 1 patient each. In a series of 8 patients with cancer with nonconvulsive SE, seizure activity was attributed to “increasing brain tumor” in 3 patients and new leptomeningeal metastases in a fourth patient.\textsuperscript{17}

Forty-three percent of patients had a history of seizures, which is consistent with reports of patients with SE of all causes.\textsuperscript{1,3-5,10} Discontinuation of or noncompliance with AED therapy is considered the greatest risk for SE in patients with epilepsy.\textsuperscript{1,4,12,13} Dependence on historical information of AED use, however, is unreliable.\textsuperscript{1,20} Barry and Hauser\textsuperscript{20} demonstrated that only 15% of patients with subtherapeutic levels of AEDs at the time of SE had previous therapeutic levels. Furthermore, 29% of patients with subtherapeutic levels had acute causes of SE. Similarly, 36% of our patients with subtherapeutic levels had acute illnesses that contributed to SE. Thus, even in the presence of a subtherapeutic level, additional workup is indicated.

### Table 4. Profile of Patients Who Died Within 30 Days of SE

<table>
<thead>
<tr>
<th>Patient/ Age, y</th>
<th>Tumor Type</th>
<th>CNS Tumor Status</th>
<th>Other Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/61 Laryngeal</td>
<td>None</td>
<td>Bilateral carotid occlusions and strokes secondary to previous radiation therapy</td>
<td>Bilateral carotid occlusions and strokes secondary to previous radiation therapy</td>
</tr>
<tr>
<td>2/52 Breast</td>
<td>Diagnosed 1 week earlier</td>
<td>Intractable SE, aspiration, hypotension, poor neurological status</td>
<td>Intractable SE, aspiration, hypotension, poor neurological status</td>
</tr>
<tr>
<td>3/33 Anaplastic astrocytoma</td>
<td>Comparison unavailable</td>
<td>Pneumonia, UTI, hypotension, desaturation</td>
<td>Pneumonia, UTI, hypotension, desaturation</td>
</tr>
<tr>
<td>4/67 Unbiopsied kidney mass</td>
<td>New</td>
<td>Multiple hemorrhagic CNS masses</td>
<td>Multiple hemorrhagic CNS masses</td>
</tr>
<tr>
<td>5/94 Unbiopsied lung mass</td>
<td>NCHCT only</td>
<td>Significant metabolic derangements at time of SE, poor neurological status</td>
<td>Significant metabolic derangements at time of SE, poor neurological status</td>
</tr>
<tr>
<td>6/52 GBM</td>
<td>Diagnosed 1 week earlier</td>
<td>SE occurred postoperatively, poor neurological status</td>
<td>SE occurred postoperatively, poor neurological status</td>
</tr>
<tr>
<td>7/59 Breast</td>
<td>Progression</td>
<td>NCHCT only</td>
<td>Decline in neurological status</td>
</tr>
<tr>
<td>8/74 Anaplastic oligo</td>
<td>NCHCT only</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous system; GBM, glioblastoma multiforme; NCHCT, noncontrast head computed tomography; oligo, oligodendroglioma; SE, status epilepticus; UTI, urinary tract infection.

### Table 5. Outcome Stratified by Histologic Features

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBM</td>
<td>Systemic Cancer</td>
</tr>
<tr>
<td>Patients</td>
<td>8</td>
</tr>
<tr>
<td>Dead*</td>
<td>5</td>
</tr>
<tr>
<td>Median survival from, mo</td>
<td></td>
</tr>
<tr>
<td>Tumor diagnosis</td>
<td>12</td>
</tr>
<tr>
<td>SE</td>
<td>7.3</td>
</tr>
<tr>
<td>Median F/U of survivors of SE, mo</td>
<td>7</td>
</tr>
<tr>
<td>Death within 30 d</td>
<td>1 (12.5)</td>
</tr>
</tbody>
</table>

Abbreviations: F/U, follow-up; GBM, glioblastoma multiforme; SE, status epilepticus.

*Patients who died as of last F/U, including those who died within 30 days.
†From diagnosis primary tumor/cerebral metastases.

### Table 4 presents the profile of the 8 patients (23%) who died within 30 days of hospital admission for SE. Of these 8, 4 died during hospitalization for SE. Twelve additional patients died at a median of 242 days following SE. Five patients were lost to follow-up and 10 patients were alive at a median of 1969 and 296 days, respectively. Table 5 displays outcome stratified by histologic features.
status epilepticus in the setting of systemic cancer was associated with higher 30-day mortality. These patients, however, were older (64 vs 52 years) and had more major acute illnesses (33% vs 20%) than those with primary brain tumors. Expected survival of patients with metastatic disease is shorter than that of those with high-grade gliomas.

Age, status of the tumor, seizure type, and history of epilepsy were not predictive of 30-day mortality. Older age, however, was associated with a worse long-term outcome, including higher rate of nursing home placement and shorter overall survival. It is well known that age is a significant prognostic factor among patients with cancer of all types.

Duration of SE, an important predictor of outcome, was not available for our patients, although in all cases SE was terminated. In the majority of our patients, a benzodiazepine and phenytoin were sufficient to terminate SE. Yet, with these interventions alone, only 60% to 70% of patients with SE of all causes respond to treatment.1,12 Lowenstein and Alldredge11 noted that patients with SE secondary to a brain tumor were among those with the best response to treatment. We speculate that the increased responsiveness of SE may have culminated in a shorter duration of SE, thereby reducing risk of death.

Our data have several limitations expected for a retrospective analysis including determination of performance status, the nature of patients’ epilepsy either before or after SE, data regarding duration of SE, description of seizure activity, and accurate ascertainment of quality of life outcomes. Patients often presented initially to outside hospitals, and thus, data regarding management of SE at the outside facility were not always available.

Statistical limitations include the relatively small sample size, which both limits the statistical power to find a difference and precludes the use of multivariate analyses such as Cox proportional hazards modeling to determine interrelationships among factors. Given limitations of the Current Procedural Terminology coding system, it is possible our search did not identify all fatal cases of tumor-related SE, which may have additionally induced bias from sample selection and/or the number of subjects.

Our study suggests that aggressive treatment of SE is indicated in patients with cancer, especially younger ones, because SE appears to be treatment responsive in this population. Recovery from the event may be more limited in older patients who frequently require subsequent nursing home placement. Workup of underlying causes of SE is indicated, even in the presence of subtherapeutic AED levels, because coexistent conditions contributing to development of SE may be present. In those with known cancer, brain imaging should be performed, because SE often occurs in the setting of tumor progression or new metastases. It also appears that mortality following SE may have more to do with the patient’s disease than the episode of SE.

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Author Contributions: Study concept and design: Schiff. Acquisition of data: Cavaliere. Analysis and interpretation of data: Cavaliere, Farace, and Schiff. Drafting of the manuscript: Cavaliere and Schiff. Critical revision of the manuscript for important intellectual content: Farace and Schiff. Statistical analysis: Farace. Administrative, technical, and material support: Cavaliere and Schiff. Study supervision: Schiff.

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REFERENCES