Tumor Type, Epilepsy Burden, and Seizure Documentation: Experiences at a Single Center Neuro-Oncology Clinic

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Clinical Study

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Abstract

Purpose: Patients with both primary and metastatic brain tumors have significant seizure burden due to their tumor. We aim to describe seizure incidence in patients seen in neuro-oncology clinical practice. In addition, as the management of tumor related epilepsy (TRE) may require collaboration between subspecialists, documentation regarding seizures and AEDs is evaluated.

Methods: This is a retrospective review of patients with a primary brain tumor or brain metastases seen in a neuro-oncology clinic in a 30 day period. A total of 356 unique patients were used in the descriptive analysis of seizure burden. 199 of these patients had TRE and were included in the analysis of seizure documentation.

Results: Of the full cohort of patients, 55.3% (197/356) had TRE. The most common primary tumor was glioblastoma (GBM) (35.7%) and the most common metastatic tumor was breast cancer (51.2% of metastatic tumors). Of all tumor types, anaplastic astrocytomas had the highest percentage of patients with TRE (42.9%).

The analysis of seizure documentation in patients with TRE revealed that the majority of notes (90.9%) mentioned seizures; however, fewer notes provided seizure frequency (51.3%), seizure descriptions (39.7%) or commented on AED regimens (58.3%).

Conclusion: This study defines a representative cohort of patients seen in neuro-oncology clinic. Among patients with TRE, details regarding seizures and antiepileptic regimens are often not documented in clinic notes. Improved documentation could facilitate further research in this population and impact patient care.

Introduction

Patients with both primary brain tumors and brain metastases have significant seizure burden due to their lesion(s), with up to 90% of patients having epilepsy as a consequence of their cancer [1–3]. Tumor related epilepsy (TRE) is also often resistant to medical management and presents a significant source of mortality and morbidity in patients with brain tumors [1–6]. Currently, the underlying mechanisms of TRE are not fully understood, although higher rates of epilepsy have been reported in patients with low grade gliomas, larger tumor volumes, frontal tumor location, and molecular markers such as the IDH1 mutation [1–5]. It is likely that tumor biology plays a role in TRE. Oncometabolites have been demonstrated to facilitate seizures in preclinical models [7]. It can also be hypothesized that direct tumor cell-neuronal interaction could comprise another mechanism [8, 9].

The management of these patients is often complex, requiring simultaneous oncological treatment (medical, radiotherapeutic, and surgical) as well as epilepsy management. As such, clear communication among expert providers is essential. Optimal treatment and management of epilepsy and the careful choice of a single agent or combination antiepileptic drug (AED) regimen requires collaboration between

neurologists and seizure specialists. The understanding of potential drug interactions of AEDs, chemotherapy and certain medications commonly utilized in patients undergoing cancer treatment. Furthermore, recognizing specific side effects related to the use of antiseizure medications is important and requires mutual understanding of treatments prescribed by the other specialists [10–15].

While brain tumor patients may frequently see multiple experts from various specialties, and these specialists may informally communicate and collaborate, there are no established best practices nor is there a consistent manner on how seizures and AED adverse effects are recorded and addressed. An important step towards improving cross-specialty collaboration is accurately characterizing and documenting the seizure burden of patients with primary or secondary tumors in the brain and central nervous system.

Improved documentation has implications both for clinical practice as well as future research. Standardized and detailed documentation of seizures at neuro-oncology clinic visits will allow for early identification of toxicities and drug interactions as well as identification and documentation of breakthrough seizures or seizure-associated symptoms. This information is needed to evaluate the efficacy of anti-seizure prophylaxis and to adapt and optimize treatment regimens. As both overly cautious prophylaxis and polypharmacy can result in a higher likelihood of medication adverse effects and under-treatment can result in breakthrough seizures, thorough documentation of patient progress is paramount.

More thorough seizure evaluation and documentation during neuro-oncology clinic visits would increase opportunities for clinical assessment of seizures and may improve documentation accuracy [16–19]. Thus adequate and accurate documentation of seizure characteristics, frequency, adherence to AED therapy and monitoring of side effects are key to management of brain tumor patients, clinical epilepsy research and longitudinal patient outcomes. Treatment side effects and effectiveness of seizure control should be distinguished from symptoms and manifestations of tumor progression, further underscoring the need for precise evaluation and documentation [19–23].

The purpose of this study is to provide a descriptive analysis of seizure incidence in patients seen in neuro-oncology clinical practice. Further, in the subset of those patients with TRE, we aim to determine documentation of seizure frequency, seizure semiology, and AED regimen within neuro-oncology clinic notes.

Methods

Patient Selection

In this retrospective review, we reviewed all patients seen at Northwestern Medicine Malnati Brain Tumor Institute neuro-oncology clinic in October 2019. Patients had to have a diagnosis of a primary brain tumor or brain metastases with one or more physical appointments with one of the six neuro-oncology physicians and three neuro-oncology nurse practitioners.

TRE was defined as patients having had a seizure occurring any time from one month prior to tumor diagnosis up to the time of the visit. Duplicate patients who had more than one visit during October 2019 had their second visit removed. This yielded 199 patients to be included in the analyses. (Fig. 1)

Variables

The tumor type, grade, and presence or absence of seizures was collected for all patients. The progress notes for each patient visit in this timeframe were reviewed. Documentation in each note was assessed for the parameters listed in Table 1. The reviewed parameters included but were not limited to description and dates of seizures, location of seizure description within the note, and medication documentation. Each variable was then analyzed for inclusion in patient charts. The time of the seizure relative to the time of the clinic visit was documented. Each variable was analyzed within subgroups of patients who had seizures within six, three, and one month(s) of the office visit, yielding 82, 65, and 43 patients respectively. Data was stored in the Northwestern University Tumor Related Epilepsy REDCap database (Grant Number UL1TR001422).

Table 1
Variables obtained from neuro-oncology clinic visit notes

Variables Evaluated for Each Patient Note
"Seizure/epilepsy/convulsion" mentioned anywhere in the note
"Seizure/epilepsy/convulsion" used in HPI
Number of seizures included in the note
Any dates of seizures included in the note
Description of seizure included in the note
Notes in which patients had focal seizures
Seizure symptoms included in the note
Lateralizing language used in the note
Luders Terminology used in the note
ILAE Terminology used in the note
Change in semiology mentioned in the note
"Seizure/epilepsy/convulsion" used in assessment/plan
"Seizure/epilepsy/convulsion" mentioned as a separate heading in problem list
AEDs listed in automatically generated medication list
AEDs commented on elsewhere in the note
No change to AED regimen based on the note
Note clearly states no change to AED regimen
Patients on prior AEDs
Note includes list of prior AEDs

Results

A total of 356 patients were seen in neuro-oncology clinic in October 2019. The majority of patients had primary brain tumors (87.9%), while 12.1% of patients had metastatic tumors. Of the full cohort of patients, 55.3% (197/356) had TRE. Patients of all age ranges were seen, with a median age of 55 and the majority of patients were female. (Table 2)

Table 2
Patient Demographics

Patient Demographics (N = 356)	Median [IQR], N (%)
Age	55 [41–65]
Gender	186 (52.2%) F
Race	
White	284 (79.8%)
Black	18 (5.1%)
Asian	15 (4.2%)
American Indian/Alaskan Native	2 (0.5%)
Other	22 (6.2%)
Declined	15 (4.2%)
Ethnicity	
Hispanic	25 (7.0%)
Non-Hispanic	314 (88.2%)
Declined	17 (4.8%)
Tumor	
Primary CNS Tumors	313 (87.9%)
Metastatic Tumors	43 (12.1%)
Tumor Related Epilepsy	199 (55.9%)

The most common primary tumor was glioblastoma (GBM, 35.7%) and the most common metastatic tumor was breast cancer (51.2% of metastatic tumors). Of all tumor types, anaplastic astrocytomas had the highest percentage of patients with TRE (42.9%). Full information on the distribution of tumor types, grade, and seizure burden can be seen in Table 3.

Table 3
Tumor Types and Seizure Burden

Tumor Type	N	Number of patients without seizures	Number of patients with seizures
Total	**356**	**159**	**197**
Meningioma	*25*	*11*	*14*
Grade II	*29*	*9*	*20*
Oligodendroglioma	15	3	12
Diffuse Astrocytoma	8	1	7
Ependymoma	6	5	1
Grade III	*49*	*7*	*42*
Anaplastic Astrocytoma	32	3	29
Anaplastic Oligodendroglioma	15	3	12
Ependymoma	2	1	1
Grade IV	*127*	*41*	*86*
Glioblastoma - IDH wild type	108	36	72
Glioblastoma - IDH mutated	19	5	14
Metastatic Tumors	*43*	*28*	*15*
Breast Cancer	22	15	7
Lung Cancer	9	6	3
Melanoma	7	4	3
Thyroid Cancer	1	1	0
Prostate Cancer	1	1	0
Cystic Adenoid Cancer	1	1	0
Endometrial Cancer	1	0	1
Dural metastasis of unknown origin	1	0	1
Other	*83*	*63*	*20*
Primary CNS Lymphoma	15	12	3
Glioma NOS (Pathology Inconclusive/ Unavailable)	13	7	6

IDH = isocitrate dehydrogenase; CNS = central nervous system; NOS = not otherwise specified

Tumor Type	N	Number of patients without seizures	Number of patients with seizures
Systemic Hematologic Malignancies	12	10	2
Pineal Tumors	5	5	0
Cerebellar Tumors	5	2	3
Hemangioma	4	2	2
Nerve Sheath Tumors	3	3	0
Neurosarcoidosis	3	2	1
Pituitary Tumors	3	3	0
Schwannomas	3	3	0
Spinal Cord Lesions	3	3	0
Tuberous Sclerosis	2	1	1
Arachnoid Cyst	1	1	0
Cavernoma	1	0	1
Germinoma	1	1	0
CNS Lesions NOS at time of visit	9	8	1
IDH = isocitrate dehydrogenase; CNS = central nervous system; NOS = not otherwise specified			

The analysis of seizure documentation in patients with TRE revealed that the majority of notes (90.9%) mentioned “seizure” at least once in the note, although was less often documented in the history of present illness portion of the note (68.8%). These rates were relatively stable regardless of the time that had passed since the seizure and the clinic visit. Fewer notes (39.7%) provided additional descriptions of the seizures. Inclusion of these descriptive characteristics was less likely as the time between a patient’s seizure and their clinic visit increased, with the lowest rates being found if the interval was greater than 6 months. The number of seizures was mentioned in approximately half of the notes and the date of the seizure was mentioned in slightly more than one-third of the notes. (Table 4)

Table 4
Tumor-related epilepsy documentation based on timing of most recent seizure relative to clinic note

	Lifetime N (%)	Six months since last seizure N (%)	Three months since last seizure N (%)	One month since last seizure N (%)
"Seizure/epilepsy/convulsion" mentioned anywhere in the note	181 (90.95)	73 (89.02)	58 (89.23)	40 (93.02)
"Seizure/epilepsy/convulsion" used in HPI	137 (68.84)	62 (75.61)	51 (78.46)	35 (81.39)
Number of seizures included in the note	102 (51.25)	40 (48.78)	32 (49.23)	21 (48.84)
Any dates of seizures included in the note	69 (34.67)	35 (42.68)	25 (38.46)	18 (41.86)
Description of seizure included in the note	79 (39.69)	43 (52.44)	39 (60)	29 (67.44)
Notes in which patients had focal seizures	49 (24.82)	30 (36.59)	27 (41.54)	21 (48.84)
Seizure symptoms included in the note	29 (14.57)	18 (21.95)	16 (24.62)	13 (30.23)
Lateralizing language used in the note	21 (10.55)	13 (15.85)	11 (16.92)	8 (18.6)
Luders Terminology used in the note	5 (2.51)	2 (2.44)	0 (0)	0 (0)
ILAE Terminology used in the note	6 (3.01)	4 (4.88)	3 (4.62)	2 (4.65)
Change in semiology mentioned in the note	8 (4.02)	5 (6.09)	3 (4.62)	2 (4.65)
"Seizure/epilepsy/convulsion" used in assessment/plan	142 (71.35)	64 (78.05)	51 (78.46)	36 (83.72)
"Seizure/epilepsy/convulsion" mentioned as a separate heading in problem list	134 (67.33)	58 (70.73)	47 (72.31)	34 (79.07)
AEDs listed in automatically generated medication list	146 (73.37)	62 (75.61)	49 (75.38)	32 (74.42)
AEDs commented on elsewhere in the note	116 (58.29)	52 (63.41)	41 (63.08)	25 (58.24)
No change to AED regimen based on the note	187 (93.97)	76 (92.68)	60 (92.31)	43 (100)

HPI = history of present illness; ILAE = International League Against Epilepsy; AED = antiepileptic drug

	Lifetime N (%)	Six months since last seizure N (%)	Three months since last seizure N (%)	One month since last seizure N (%)
Note clearly states no change to AED regimen	94 (47.23)	33 (40.24)	27 (41.54)	18 (41.86)
Patients on prior AEDs	47 (23.62)	15 (18.29)	12 (18.46)	7 (16.28)
Note includes list of prior AEDs	9 (4.52)	3 (6.66)	3 (4.62)	1 (2.33)
HPI = history of present illness; ILAE = International League Against Epilepsy; AED = antiepileptic drug				

The frequency with which antiepileptic medications were mentioned in the note remained relatively stable in each follow up note after the first seizure was documented. The majority of notes (93.9%) did not document a change in AEDs in the automatically generated medication list. However fewer notes (47.2%) directly stated that there was no change in AED in typed portions of the note. Similarly, mention of prior AED regimens were reported in a minority (23.6%) of notes, with a list of prior AEDs rarely included (4.5%).

Seizure semiology, terminology as recommended by Luders et al [24], and ILAE classification were rarely included in patient notes at any time point. (Table 4)

Discussion

Results of a descriptive study of TRE documentation in a neuro-oncology clinic are presented. It is in concordance with previously published data in terms of neuro-oncology clinic patient tumor type frequency, with GBM being the most frequent primary tumor and metastatic breast and lung cancer and melanoma being the most common metastatic tumor types [25, 26]. It is also in line with current literature demonstrating significant seizure burden in lower grade gliomas, and that IDH mutated GBM have a higher TRE incidence when compared to IDH wild type GBM.

Our study is one of the first to define the proportion of patients with TRE in a neuro-oncology clinic setting. Fifty-six percent of patients seen in our cohort had TRE, with 36.7% having had a seizure within 6 months of their clinic visit. As such, we demonstrate a significant proportion of neuro-oncology patients requiring active seizure surveillance and management. This underscores the centrality of collaboration across specialties, and specifically between neuro-oncologists and epileptologists, to care of patients with TRE.

The majority of notes for all patients seen in the neuro-oncology clinic do include the words “seizures,” “epilepsy,” or “convulsion.” However, details regarding seizure semiology and AED regimen are missing in the majority of documentation.

Changes in frequency and seizure semiology have been described in association with tumor progression [19–23, 27]. This has led to calls for systematic evaluation of seizures in those with tumor related epilepsy and further study into correlating seizure activity with treatment response [20, 21]. However, without improvement and standardization of seizure documentation, successful utilization of seizures as an outcome measure will not be possible. Similarly, without adequate and detailed baseline information on seizure aura, frequency, focality, and lateralization, changes from baseline cannot be accurately assessed.

There are significant gaps in our understanding of TRE, including mechanisms, role of seizures in the oncologic course, and relationship of seizures to prognosis. Furthermore, recommendations on management, both medical and surgical, for TRE exist, but are limited by the current, incomplete state of understanding of TRE [1–9]. A clear understanding of the current frequency of seizures and seizure semiology is beneficial for future improvements in the utility of seizures as a clinical trial endpoint and potentially more importantly the complex interactions between tumors and their surrounding neuronal environments.

Notably, standardized tools to improve seizure documentation exist [18, 28]; however these tools are meant for epilepsy specialists. Although TRE is significant and an important potential outcome measure of tumor management, epilepsy is often not the primary concern of the neuro-oncologist, and existing tools are thus not appropriate in scope. There is a clear need for a standard tool for seizure documentation that notes appropriate details about frequency and semiology, but that is also readily usable and able to be incorporated in the limited time available during neuro-oncology visits. Such a tool could also be generalized to non-epilepsy specialties in which seizures are commonly seen, such as post-stroke epilepsy, and may also be of value to general practitioners who care for patients with known seizure disorders. A tool designed to quickly and accurately characterize a patient's seizures would be beneficial for neuro-oncologists' evaluation of a patient's tumor progression without requiring the use of additional imaging.

This study has limitations. As this was conducted in a single institution generalizability to other hospitals and clinics may be limited. Further, the limited duration of assessment may not reflect the clinical picture over the course of the year. Finally, the excluded notes for patients who had multiple visits during October 2019 may differ in thoroughness of documentation

As this study focused on office notes from the visits in question, other forms of communication, including telephone encounters or MyChart messages where providers may have entered more specific information regarding patients' seizures, were not accounted for in this study. Also, as with any study on chart documentation for multiple physicians, note styles differ from physician to physician, making classification of location within a note not completely objective when some physicians' notes are not separated in a classic format.

Conclusion

This study defines a representative cohort of patients seen in neuro-oncology clinic and characterizes their tumor types and seizure incidence. Among patients with TRE, our study also analyzes seizure documentation within neuro-oncology clinic notes. Without a standardized documentation practice, our study shows that documentation can be improved, which would facilitate further analysis of impact on patient care as well as future research within TRE.

Declarations

Conflict of Interest:

The authors declare that they have no conflicts of interest

Ethics approval:

Institutional IRB approval was waived as this study was a retrospective quality improvement project

Consent to participate:

Consent to participate was waived as this study was a retrospective study with no more than minimal risk to patients

Funding:

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Author Contributions:

All authors contributed to the study conception and design. Material preparation and data collection were performed by Omar Bushara, Alex Guzner, and Elizabeth Bachman. The first draft of the manuscript was written by Omar Bushara and Alex Guzner. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Transparency:

All data and materials support our published claims and comply with field standards

Code Availability:

Not applicable

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Figures

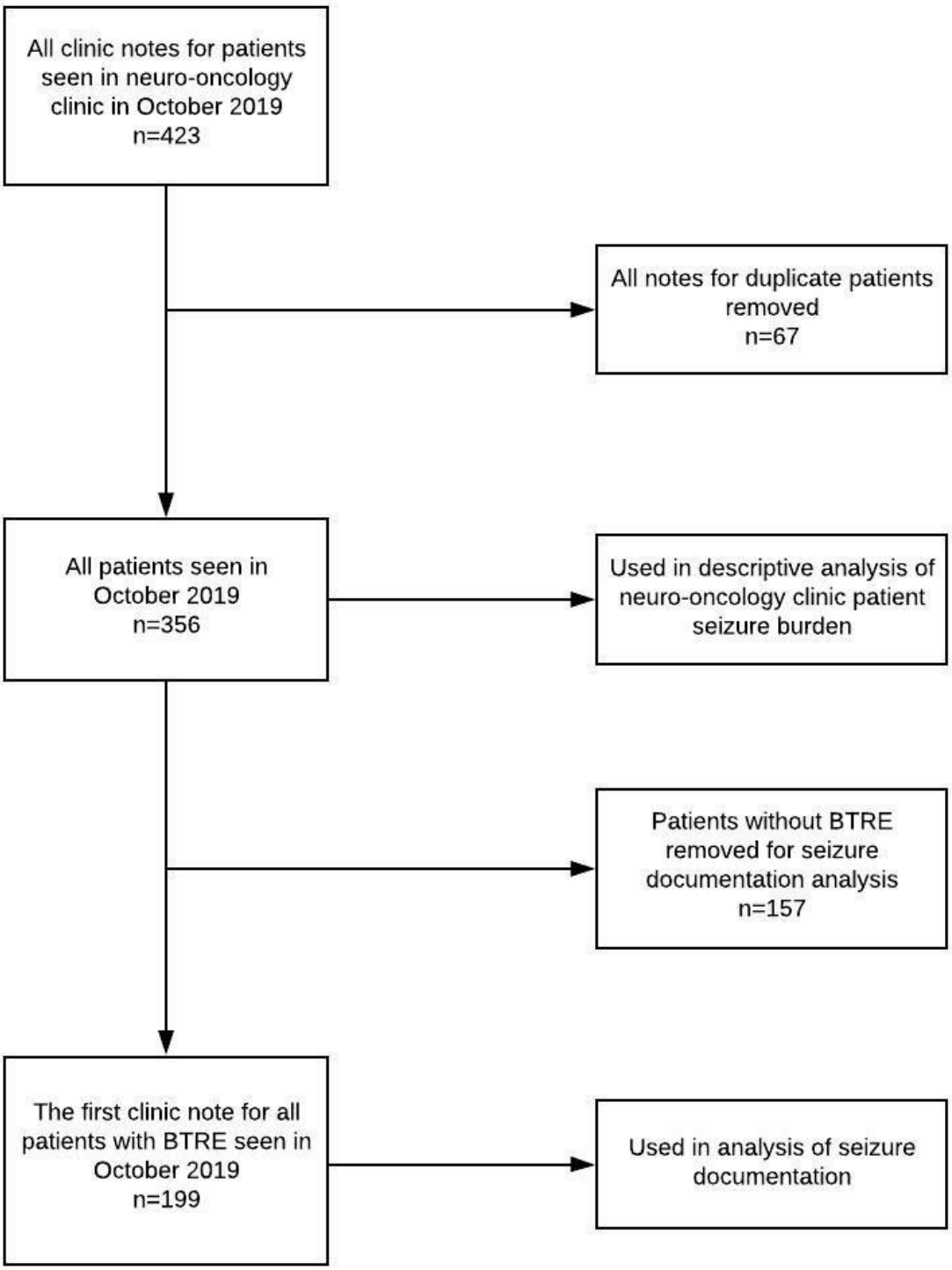

Figure 1

A total of 423 clinic notes were completed in the neuro-oncology clinic in October 2019. 67 of these notes were based on visits of duplicate patients. For duplicate patients, the first note was kept, and subsequent notes were not used in the analysis. Notes for which the primary purpose of the visit was to administer treatment or to provide treatment education rather than a full clinical evaluation were not utilized in our analysis. A total of 356 unique patients were used in the analysis of tumor types and seizure burden. Of

these patients, 157 patients did not have TRE and were thus removed for the final analysis of seizure documentation. The remaining 199 patients were included in the analysis of seizure documentation.