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Tumor-associated status epilepticus in patients with glioma: Clinical characteristics and outcomes

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ABSTRACT

Between 3 and 12% of all adult status epilepticus (SE) are caused by a brain tumor. Gliomas, and in particular, high-grade gliomas (HGGs), are at high risk of SE development. In this study, we aimed to describe the clinical characteristic and outcomes of tumor-associated SE (TASE) in a population of adult patients with glioma prospectively collected between 2013 and 2019. In the aforementioned period, we observed 26 TASE (median age: 68 years). Overall, 22 patients (85%) presented a HGG (one anaplastic astrocytoma and 21 a glioblastoma) while 4 had a LGG (two diffuse astrocytoma and two gangliolioma). All the lesions were supratentorial, and the temporal lobe was the most frequently involved (20 patients). Fourteen patients (54%) had the SE episode as the first manifestation of the tumor; in the remaining 12 (all patients with a HGG), the development of SE heralded tumor progression or reappearance. When TASE outcomes were compared with the ones observed in the general population of SE (SEGP), the response to treatment was not different between the two populations (refractory SE (RSE)/super-refractory SE (SRSE) 12% versus 13%, $p = 0.75$). In the short-term, group with TASE had a significantly lower global disability (modified Rankin scale (mRS) < 3 at discharge: 60% versus 32%, $p < 0.001$; at 30 days follow-up: 62% versus 30%, $p < 0.001$) and mortality (30 days mortality: 4% versus 27%, $p = 0.008$). Six months and 1 year mortality did not show any difference between the two groups (6 months: 46% and 45%, respectively, $p = 0.9$; 1 year: 68% and 52%, respectively, $p = 0.22$).
The appearance of TASE often heralds tumor grow and progression. Even in this context, it appears to be as treatment-responsive as SEGP and the short-term disability and mortality related to SE episode are lower than those observed in the SEGP.
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1. Introduction

Epilepsy is very common in patients with primitive or secondary brain tumors (named tumor-associated epilepsy, TAE), and it determines a high burden of the disease. The risk of epilepsy development, either as the tumor presenting symptoms or later in the disease course, varies deeply among different neoplasm mostly depending on the tumor's type but also on tumor's location (highest risk carried by cortical lesions involving the temporal and insular cortex). It is known that the risk is inversely proportional to the World Health Organization (WHO) tumor grade with the lower grades carrying a greater risk than the higher ones [1,2]. Thus, among primitive brain tumors, the highest risk is found in neuronal–glial tumors: dysembryoplastic neuroepithelial tumor (DNET) has a risk of 100% and ganglioglioma of around 80–90%. Among astrocytic and oligodendroglial tumors, low-grade gliomas (LGGs) such as low-grade astrocytoma and oligodendroglioma have a risk between 60 and 85% while high-grade gliomas (HGGs) such as glioblastoma multiforme (GBM) have a risk between 30 and 50% [3]. Epileptogenicity in brain tumors is based on several mechanisms and is probably multifactorial. Tumors that have a slow growth let the adjacent and remote brain parenchyma to have enough time to make changes associated with epileptogenesis, while this is not the case in fast-growth tumors where epilepsy is mostly caused by tissue damages (necrosis and hemosiderin's deposition). Moreover, in more recent years, there are increasing evidences that genetic biomarkers could play important roles in the development of glioma-associated epilepsy [1,4].

In the general population, between 3 and 12% of all adult status epilepticus (SE) are caused by a brain tumor (tumor-associated SE (TASE)) [5–7]. Status epilepticus is indeed a life-threatening medical emergency.

Abbreviations: TAE, tumors-associated epilepsy; TASE, tumor-associated status epilepticus; SEGP, status epilepticus in the general population; NOS, not otherwise specified; HGG, high-grade glioma; LGG, low-grade glioma.

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The Commission on Classification and Terminology and the Commission on Epidemiology of the International League Against Epilepsy (ILAE) have recently proposed a new definition of SE: it is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures and it is a condition which can have long-term consequences, including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures [8].

Between 15 and 22% of patients with TAE develop TASE. The risk appears to be directly proportional to tumor WHO grade. Thus, patients with HGG appear particularly predisposed to develop TASE. This finds explanation either in macroscopic changes induced by the destructive nature of these tumors (e.g., blood–brain barrier breakdown, cerebral edema, necrosis, hemorrhage and hemosiderin deposition) or in microscopic changes that happen in the parenchyma near the tumor lesion (e.g., increased expression of multidrug resistance proteins, reduced expression of gamma-aminobutyric acid (GABA) and glutamate receptors, decreased myo-inositol levels) [9].

Moreover, it is also possible that chemotherapeutic drugs, more frequently used in patients with HGG compared with patients with LGG, can adversely affect anti-epileptic drugs (AED) levels easily leading to TASE development [9].

The existing studies on SE in patients with glioma are scarce and confounded by a number of factors: the great part is retrospective, based on small sample size, and they frequently include different cranial tumor types and grades without differentiating them [9].

In this study, we aimed to describe the clinical characteristic and outcomes of TASE in a population of adult patients with glioma and make a comparison with the SE in the general population (SEGP).

2. Methods

2.1. Type of study

This is a retrospective analysis on the subpopulation with glioma TASE belonging to the consecutive adult patients with SE (≥14 years old) prospectively collected during a five-year period (from September 1st 2013 to March 31st 2019) at the Ospedale Civile Baggiovara (OCB), Modena, Italy. A comparison of the most important clinical and prognostic characteristics of these patients and the nonhypoxic SE was then performed.

2.2. Definitions adopted

Since this SE collection begun in 2013, for cases collected between 2013 and 2015, the definition of SE adopted was that of a continuous seizure or two or more discrete seizures between which there is no complete recovery of consciousness lasting ≥5 min for convulsive SE (CSE) [10]. Whereas in cases of nonconvulsive SE (NCSE), which means a SE episode not accompanied by prominent motor phenomena or with subtle motor phenomena, a 30-minute cutoff time was adopted. In 2015, the new definition of SE was published [8]. The SE was then defined as a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms that lead to abnormally prolonged seizures (after time point t1) that could have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the time and duration of seizures. Based on evidences from animal studies, time point 1 has been set to 5 min for tonic–clonic SE, 10 min for focal SE with impaired consciousness, and 10–15 min for absence SE.

Thus, SE episodes collected after 2015 were judged to be a SE according to the time point 1 of the new definition, as reported above.

Glioma–TASE was defined as an episode fulfilling the definition of SE presenting either in patient with a known cerebral glioma or as the first manifestation in newly diagnosed cerebral glioma and in which the SE episode was judged to be progressive symptomatic of this condition or multifactorial in the context of a concomitant acute precipitating factor.

According to the internationally agreed definitions [11], a SE was considered refractory (RSE) if it needed the admission to the intensive care unit (ICU) and it resolved after the administration of anesthetic therapy; it was considered super-refractory (SRSE) if it persisted despite the anesthetic therapy or it recurred after at least 24 h of anesthetic treatment or at its reduction.

Tumor progression was defined as the appearance of radiographic changes known to be related to tumor progression when compared with the previous neuroimaging studies acquired in that patient.

2.3. Inclusion and exclusion criteria

We included all the adult patients (≥14 years old) with a SE episode caused by a cerebral glioma. Patients with primitive cerebral tumors different from glioma and patients with cerebral metastasis were excluded. The population compared with glioma–TASE was composed of all consecutive patients experiencing a SE provoked by an etiology different from cerebral tumors. Patients with postanoxic SE were excluded.

Patients presenting two or more SE episodes during the study period were considered only for the first episode to avoid the bias of repeated measurements in one subject.

2.4. Procedures and endpoint

We created a specific "Status Epilepticus Form" to collect, for each case, the information needed as previously explained [12,13]. Any missing information was then added by the consultation of the hospital informatics database. The histopathological and molecular tumor profiles were extracted by the consultation of the clinical pathology informatics database. For each patient, any acquired neuroimaging study (computed tomography (CT) and magnetic resonance imaging (MRI)) was reviewed by the authors to better define the exact location and characteristics of the lesion.

The information collected for each patient were as follows: age, gender, history of epilepsy prior to SE, level of disability before SE (classified using modified Rankin scale (mRS)), type of SE, histopathological and molecular characteristics, neuroimaging characteristics, timeframe between the diagnosis of cerebral tumor and SE onset, oncological treatment (chemotherapy, radiotherapy, or surgery) before SE, duration and dosage of AED used to treat the SE episode, anesthetic drugs, and other therapies used. Follow-up pieces of information, obtained from the consultation of the hospital informatics database, were as follows: level of disability at hospital discharge and at 30 days follow-up and 30 days and 6 months mortality.

The primary study endpoints were to define the clinical characteristics, the treatment response, the short-term level of disability (30 days), and the short-term and long-term mortality (30 days up to 6 months) of the population with glioma–TASE. The secondary endpoint was to make a comparison of these characteristics with those of SEGP.

Our institutional review board approved the study.

2.5. Statistical analysis

The statistical analysis was performed using Statistical Package for Social Science (SPSS) software. Continuous values were compared using the independent samples t test. Categorical variables were compared using the Pearson χ^2 test or the Fisher exact test, where required. The statistical significance cutoff was set at 0.05.

3. Results

3.1. Clinical characteristics of glioma–TASE

During the study period, we observed 496 episodes of SE in 440 patients. Among these patients, 26 (6%) experienced a SE episode symptomatic of a cerebral glioma (median age: 68 years, males 15, 58%). Nineteen patients presented a focal NCSE (73%) either as an evolution from a previous convulsive form of SE (5 generalized convulsive status epilepticus (GCSE) and 2 focal convulsive status epilepticus (FCSE)) or as the only manifestation without any motor phenomenon before (12). In nine patients (35%), the follow-up electroencephalograms (EEGs) acquired in the days immediately after the SE ends showed lateralized periodic discharges (LPDs), sometimes observed for many days.

All the neoplastic lesions were supratentorial, mostly involving more than one lobe. The temporal lobe was the most frequently involved (20 patients) followed by the parietal (11), frontal (6), and occipital (5). Sixteen patients (62%) showed a lesion and a SE involving the left hemisphere, 9 in the right, and 1 bilateral.

During the study period, 3 patients experienced a SE relapse, thus, the relapsing rate was 12%.

Concerning the time at onset of SE during the tumor course, 14 patients (54%) had the SE episode as the first manifestation of the neoplasm leading to the tumor diagnosis. Overall, 20 out of 26 patients (77%) experienced the SE episode within six months from glioma diagnosis.

Analyzing the 12 patients that had already had a diagnosis of cerebral tumor (all patients with a GBM diagnosis), all have been treated with neurosurgery (but the surgery was not radical); 7 received one or more chemotherapy cycles, and 9 pan-encephalic radiotherapy. The time interval between the neoplasm diagnosis and SE appearance varied between 9 days and 23 months and, on average, was 4 months. In all the patients who experienced SE in already diagnosed cerebral tumor, the SE uncovered tumor progression or reappearance.

Nine patients had a prior history of TAE, and they were already on AED therapy (levetiracetam was the most frequently chosen AED in these patients). Moreover, three of them had already experienced a previous SE episode.

The most important clinical characteristics of the population with glioma–TASE are summarized in Table 1.

Table 1
Clinical characteristics of glioma TASE patients

Clinical characteristics			n, (%)
Total			26 (100%)
Age (median)			68 y/o
Gender		M	15 (58%)
Type of glioma		Ganglioglioma	2 (8%)
		Diffuse astrocytoma	2 (8%)
		Anaplastic astrocytoma	1 (4%)
		Glioblastoma	21 (80%)
Cerebral location	Lobes	Frontal	6 (23%)
		Parietal	11 (42%)
		Temporal	20 (77%)
		Occipital	5 (19%)
	Hemispheres	Right	9 (35%)
		Left	16 (61%)
		Bilateral	1 (4%)
Time at SE onset		As tumor presenting symptom	14 (54%)
Time between tumor diagnosis and SE		Mean	4 months
		Min–Max	9 days–23 months
TAE before TASE			9 (35%), 3 with previous SE episodes
Relapses of SE during the study period			6 (12%)
Type of SE		GCSE	1 (4%)
		FCSE	6 (23%)
		GCSE–NCSE	5 (19%)
		FCSE–NCSE	2 (8%)
		NCSE only	12 (46%)
Tumor treatment before SE (n = 12)		Neurosurgery	12
		Chemotherapy	7
		Radiotherapy	9

M: males; TAE: tumor-associated epilepsy; TASE: tumor-associated status epilepticus; GCSE: generalized convulsive status epilepticus; FCSE: focal convulsive status epilepticus; NCSE: nonconvulsive status epilepticus.

3.2. Histopathological and molecular classification of glioma

The diagnosis was pathologically confirmed in all cases. Histopathological information was available for all patients while molecular analysis for further classification and for better prognostic definition was not available for all patients since these analyses have been increasingly made only in recent years at our institution.

According to the WHO classification of the tumors of the central nervous system [14], 24 patients had a diagnosis of diffuse astrocytic or oligodendroglial tumors, and two patients had a neuronal–glial tumor. Overall, 22 patients (85%) presented a HGG while 4 had a LGG.

Going into details, two patients had a diffuse astrocytoma (grade II) not otherwise specified (NOS), one had an anaplastic astrocytoma (grade III) IDH1/2 (isocitrate dehydrogenase) wild type, 21 had a glioblastoma (grade IV) – 7 of them IDH1/2 wild type, as it is in the novo GBM, and 14 a NOS – and two had a ganglioglioma (grade I). The analysis of the codeletion 1p/19q was available just for three patients (two GBM and one anaplastic astrocytoma): in all of them, the codeletion was absent, and they were all IDH1/2 wild type, too. The analysis of methylguanine DNA methyltransferase (MGMT) promoter methylation status showed the presence of the methylation in 4 patients (3 GBM and one anaplastic astrocytoma) and its absence in 7 (all GBM) while for the other patients, the information was not available.

The small population, the high prevalence of HGG, and the few molecular information prevent us to make further correlation analysis between the epilepsy/SE clinical characteristics and the histology and molecular tumor profiles.

3.3. Comparison of morbidity, mortality, and response rate of glioma-related TASE and SEGP

We compared the characteristics of glioma–TASE (26 patients) and SEGP. The SEGP group consisted 340 patients after having excluded the SE in the context of a postanoxic encephalopathy and the primitive and secondary brain tumors.

To summarize, there are some significant differences between the two populations. Demographically, the population with glioma–TASE was younger (68 versus 76, $p = 0.003$), and the predominant gender was male (58% and 36%, respectively, $p = 0.03$). The response to treatment was not different between the two populations, meaning, that TASE was not more refractory than SEGP (RSE/SRSE 12% versus 13%, $p = 0.65$) (Fig. 1).

The two groups had a comparable level of disability (measured with the mRS) before SE while the short-term morbidity (at discharge and at 30 days from SE onset) showed that the group with TASE had a significantly lower global disability (mRS < 3 at discharge: 60% versus 32%, $p < 0.001$; at 30 days follow-up: 62% versus 30%, $p < 0.001$). Thus, the TASE returned to the level of disability present before the SE more than SEGP (62% versus 40%, $p = 0.04$) (Fig. 2).

The 30 days mortality appeared significantly lower in TASE than in SEGP (4% versus 27%, $p = 0.008$) while the 6 months and 1 year mortality were not different between the two groups (6 months: 46% and 45%, respectively, $p = 0.9$; 1 year: 68% and 52%, respectively, $p = 0.22$) (Fig. 3).

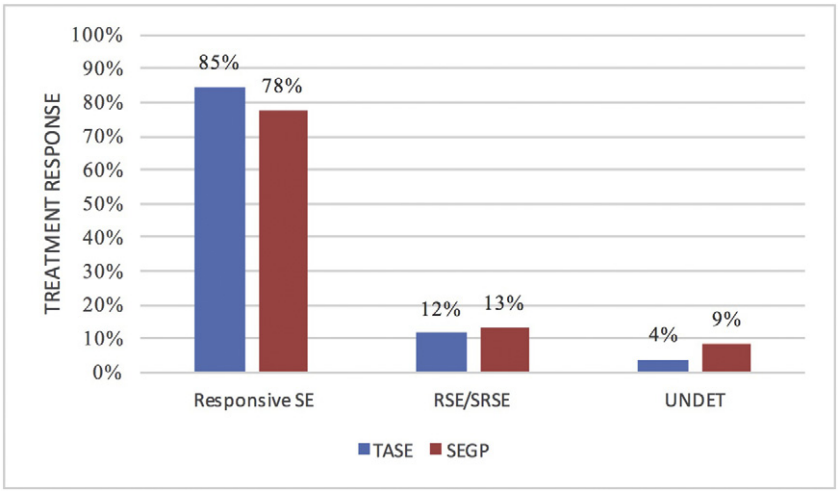

Fig. 1. Response to treatment in the TASE and in the SEGP. The TASE showed the same treatment responsiveness as the SEGP.

4. Discussion

Brain tumors are the cause of SE in 3–12% of the adult patients. It is known that gliomas, especially HGG, are the primitive brain tumors at the highest risk of SE development. In our series, 6% of patients experienced a SE caused by a glioma. If we add to these the cases of SE caused by other primitive brain tumors and brain metastasis, we overall observed 48 cases that account for 11% of all the entire population. These results are aligned with the results from previous studies [5–7]. Moreover, it seems that SE, especially NCSE, could be underestimated in patients with tumor SE [15].

As previously reported [16,17], when compared with the general population, glioma was significantly more frequent in males, and patients with glioma were younger. This was observed in our study, too. Our population is mostly formed by HGG (85%; 21 GBM and one anaplastic astrocytoma). This high presence of HGG compared with LGG, as previously reported [16,17], is due to the high frequency of SE in adult patients with HGG, thus, this is completely expected and explained. Regarding the tumor location, we found that the most frequently involved lobe was the temporal one while in a previous series, the parietal lobe was reported to be the most frequent location [18]; moreover, 62% of the cases were located in the left hemisphere as it was already reported [16]. In a previous review on brain tumor-associated SE [9], a high incidence of TASE in tumor of frontal location was reported. However, this study did not distinguish the type of the tumor.

Dealing with SE type, in our population, the majority of patients presented a focal NCSE, and only 6 patients had a GCSE (with or without evolution to a NCSE form). This is in contrast with a previous study

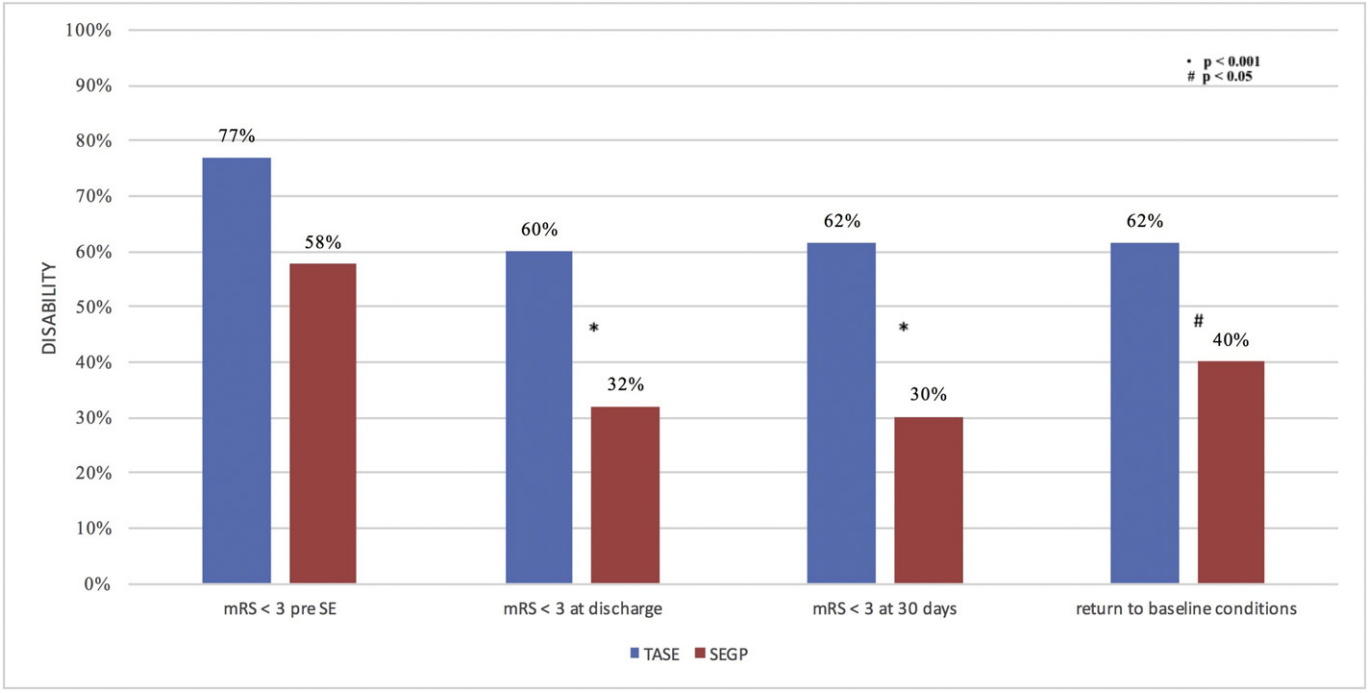

Fig. 2. Short-term disability in the TASE and in the SEGP. The TASE and SEGP groups had the same level of disability before SE. At hospital discharge and at 30 days from SE, TASE had a significantly lower disability level compared with SEGP. Thus, the proportion of patients that regained the same disability level present before SE was higher in TASE than in SEGP.

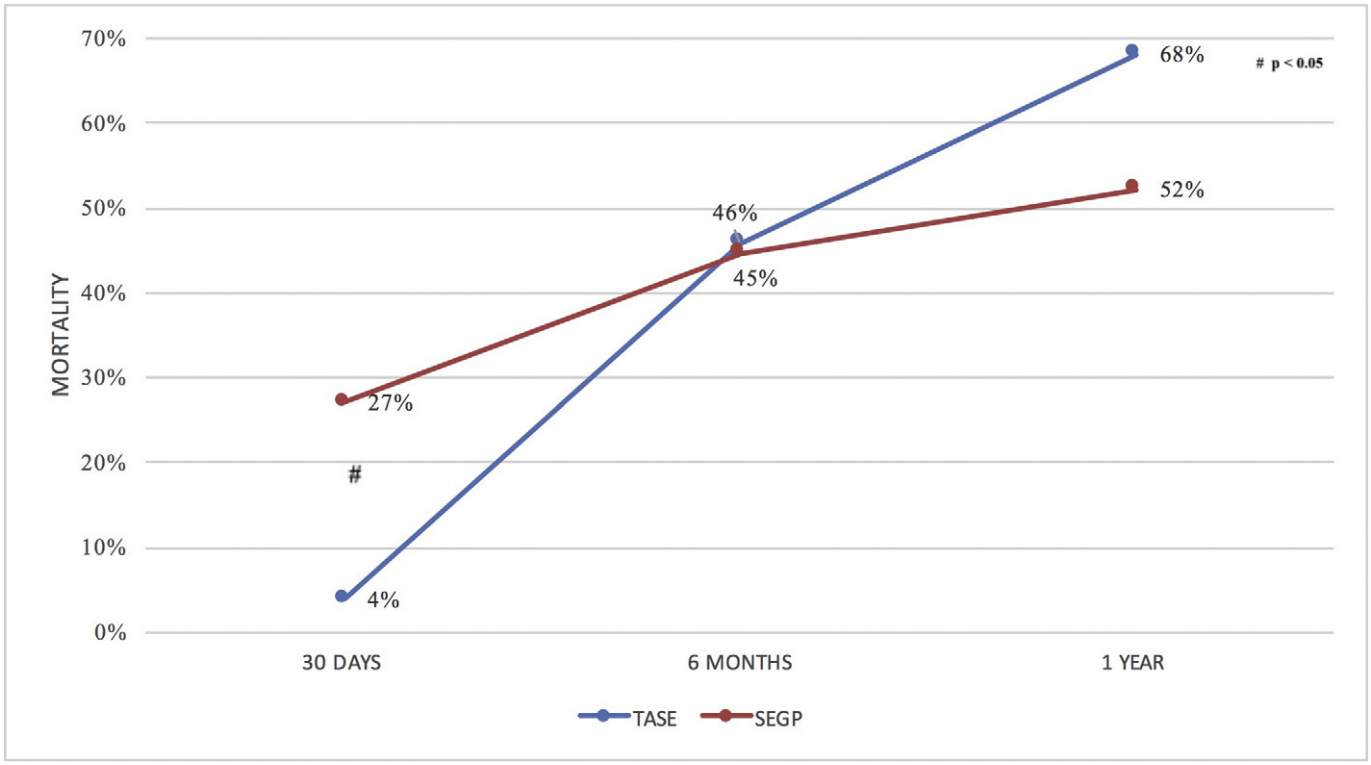

Fig. 3. Short- and long-term mortality in the TASE and in the SEGP. Tumor-associated SE showed a significantly lower 30-day mortality than SEGP. In the long-term, the mortality of the two groups were not different.

[16] in which 48% of patients had a secondarily generalized SE. Nevertheless, in previous studies, there are also evidences of a high prevalence of NCSE without coma in patients with brain tumors [19].

In more than half of the glioma–TASE, the SE episode was the first clinical manifestation of the tumor leading to its diagnosis. Overall, in 77% of patients, the SE happened at tumor diagnosis or very early in the disease course (within 6 months from the diagnosis). This is probably related to the high prevalence of HGG in this cohort even if in a previous study based on a population with a high prevalence of HGG too, a history of epilepsy before SE diagnosis was reported in 80% of patients [16]. Moreover, as previously reported [9,17,20], it appeared that TASE was more likely to occur later in the disease course but in concomitance to tumor progression. In all our patients with a known tumor diagnosis, the SE heralds a progression of the underlie neoplastic pathology.

More than 80% of SE were treatment-responsive as previously reported [15]. In the present study, TASE was as responsive to treatment as SEGP even in the presence of evidences of tumor progression as it was reported by Knudsen-Baas et al. [16]. In a previous review on TASE, refractoriness was reported to be between 14 and 18% [9].

We observed a 30-day worsening of clinical condition compared with the conditions observed before SE in 38% of the population with TASE. In a previous study [16], neurologic sequelae were reported in 30% of glioma-associated TASE at 3 months. Comparisons between our study and this study appear to be difficult because the time point and the methods of follow-up were different.

We observed a 30-day mortality of 4% that was significantly lower to that observed in SEGP. The TASE 30 days mortality observed in our population was lower than previously reported in glioma–TASE (between 14 and 20%) [16,17]. In a review on the comparison of the short-term prognosis of TASE from different tumors versus SEGP [21], the average 30 days mortality in TASE was 17% (ranging from 12 to 36%), and this was significantly worse than that of SEGP after the exclusion of patients with hypoxia (6.5%). In another subsequent review [9], the 30 days mortality of TASE and SEGP was found to be similar (23% and 20%, respectively).

Comparison with these considered studies and the present one is not possible because all of them reported the mortality in brain tumors without differentiating tumor types.

In our study, the short-term mortality related to the SE per se was very low and significantly lower than that of the general population. This should be probably related to the younger age of the group with TASE compared with SEGP. The mortality significantly increased at the long-term follow-up because of the course of underline pathology.

5. Limitations of the study

This is a retrospective analysis of a prospectively collective patients. This clinical study is based on a small population of adult patients with glioma-related SE, thus, we do not have a complete overview of all patients with glioma (meaning with and without history of SE and seizures), and this prevents us to define the incidence of SE in the population with glioma. The small population, the high prevalence of HGG, and the few available molecular information prevent us to make further correlation analysis between the epilepsy/SE clinical characteristics, treatment response, and the tumor histology/molecular profiles.

6. Conclusions

Glioma-associated TASE is not an infrequent condition, especially in HGG, presenting either at the tumor diagnosis or during the tumor course thus frequently revealing a tumor progression. Even in the context of evidences of tumor progression, TASE appears to be as treatment-responsive as SEGP. The patient admission to the ICU and the administration of anesthetic therapy is, thus, seldom required. Moreover, even in the presence of a clear tumor progression, the presence of SE could worsen the patient quality of life. Mortality and morbidity are not increased after SE episode, and they are more related, in the long term, to the natural tumor history. Given that, we encourage to fully treat patients with TASE even in a palliative setting to prevent the worsening of their quality of life.

As it has been perfectly underlined in the last WHO classifications of the brain tumors, in recent years, it appeared more and more evident that the prognosis and the tumor treatment response as well as the risk of epilepsy development and probably the AED response are based not only on the histopathological differences, but also, and probably mostly, on the biomolecular profile. This could have important clinical implications in the epilepsy treatment of these patients. To date, there is no consensus about which AED is the most effective in treatment of these patients and scarce are the information of the influence that AED therapy has on tumor chemotherapy response. Tailoring the epilepsy treatment to the tumor type could potentially prevent SE development and reduce the overall burden of the disease. At present, the available pieces of information on this important aspect are still scarce. Moreover, there are no studies addressing the specific problem of the influences of biomolecular profile on SE development and characteristics. These are important aspects that must to be addressed in future studies.

Declaration of Competing Interest

Stefano Meletti received research grant support from the MOH, he has received personal compensation as a scientific advisory board member or honoraria for speeches by UCB and Eisai. Other authors report no disclosures.

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