



Management of epilepsy in brain tumors

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Abstract

Epilepsy in brain tumors (BTE) may require medical attention for a variety of unique concerns: epileptic seizures, possible serious adverse effects of antineoplastic and antiepileptic drugs (AEDs), physical disability, and/or neurocognitive disturbances correlated to tumor site. Guidelines for the management of tumor-related epilepsies are lacking. Treatment is not standardized, and overall management might differ according to different specialists. The aim of this document was to provide directives on the procedures to be adopted for a correct diagnostic-therapeutic path of the patient with BTE, evaluating indications, risks, and benefits. A board comprising neurologists, epileptologists, neurophysiologists, neuroradiologists, neurosurgeons, neuro-oncologists, neuropsychologists, and patients' representatives was formed. The board converted diagnostic and therapeutic problems into seventeen questions. A literature search was performed in September–October 2017, and a total of 7827 unique records were retrieved, of which 148 constituted the core literature. There is no evidence that histological type or localization of the brain tumor affects the response to an AED. The board recommended to avoid enzyme-inducing antiepileptic drugs because of their interference with antitumoral drugs and consider as first-choice newer generation drugs (among them, levetiracetam, lamotrigine, and topiramate). Valproic acid should also be considered. Both short-term and long-term prophylaxes are not recommended in primary and metastatic brain tumors. Management of seizures in patients with BTE should be multidisciplinary. The panel evidenced conflicting or lacking data regarding the role of EEG, the choice of therapeutic strategy, and timing to withdraw AEDs and recommended high-quality long-term studies to standardize BTE care.

Keywords Epilepsy · Brain tumors · Antiepileptic drugs · Quality of life · Side effects · Interaction

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Introduction

Brain tumors (BT) account for 1–2% of all tumors in adults and are considered rare tumors [14, 29, 102, 151]. Their global incidence is 18.7 cases per 100,000 inhabitants/year [29, 102]. The incidence is 11.5 cases per 100,000 inhabitants/year for benign tumors and 7.19 cases per 100,000 inhabitants/year for malignant tumors [29, 102]. Brain metastases account for 9–17% of all tumors [29] and are one of the most common neurological complications of systemic tumors. Epileptic

seizures occur in 20–40% of patients with brain metastases, especially if multiple.

Epilepsy symptomatic of brain tumors (BTE) constitutes 6–10% of all cases of epilepsy and 12% of acquired epilepsy and is the most common symptom in patients with BT [90]. Epilepsy is the onset symptom in 20–40% of patients, while in a further 10% it will appear during the course of the disease [5, 121]. In overall, the frequency of epileptic seizures in patients with BT varies from 35% to 70% [37, 143].

Epilepsy in patients with BT is considered the most important risk factor for long-term disability [85, 90]. The disability caused by BTE significantly aggravates the consequences of the oncological disease and implies social and individual costs. These could be avoided, reduced, or at least controlled by preventive measures, with correct use of therapies for seizure control, as well as simply through education for the proper management of seizures by caregivers and other people close to patients (family members and workers). Choosing the proper antiepileptic drug is extremely important because patients with BTE represent a sum of many challenges—therapeutic, support, and psychosocial—that result from treating an individual who has two serious pathologies simultaneously: on the one hand, the brain tumor, and on the other hand, epilepsy. In fact, BTE patients may require medical attention for a variety of unique concerns: epileptic seizures, possible serious adverse effects of antineoplastic and antiepileptic drugs, physical disability, and/or neurocognitive disturbances correlated to tumor site [90]. There are studies on the management of nononcological epilepsy and BTE [14, 31, 43, 52, 109]. However, national and international guidelines for the management of BTE are lacking [23, 52, 53, 71]. In Italy, BTE is often underdiagnosed and managed by different specialists, including neurologists, neuro-oncologist, neurosurgeons, epileptologists, or radiotherapists, without effective coordination [91]. During the course of the disease, psychological, cognitive, and rehabilitation treatments can be added, making a multidisciplinary approach needful. The need to create a common approach based on shared discussion and a *team* culture is therefore evident and would not only benefit the patient but also would reassure all the specialists involved, who could benefit from the shared discussion. The present document is aimed at providing directives on the procedures to be adopted for a correct diagnostic-therapeutic path of the patient with BTE, evaluating indications, risks, and benefits. Specific objectives are the following:

- To evaluate the diagnostic tests used in epilepsy for the recognition and early treatment of the disease in BTE
- To determine the overall management of the antiepileptic treatment in BTE

Methods

A working group was established within the study group of BTE of the Italian League Against Epilepsy (LICE) and comprising neurologists, epileptologists, neurosurgeons, neuroradiologists, neuro-oncologists, neuropsychologists, and neurophysiologists. The board also comprised delegates of the patients' association "Blaze-Matteo Blasi". All members contributed to the identification of problems arising in the diagnostic-therapeutic process of BTE (Appendix 1). All board members were representatives of the Italian League Against Epilepsy and of the Italian Neurological Society (SIN). The diagnostic and therapeutic problems identified were converted into 17 questions structured according to the principals of Evidence Based Medicine (population, intervention, comparator, outcome (PICO)). Some questions comprised different subquestions, all listed in Table 1. The questions were discussed and, where necessary, modified during a meeting of the BTE study group. A thorough literature search was performed in July 2017 and updated in November 2017, consulting the National Library of Medicine's MEDLINE (PubMed interface) and Embase and Cochrane Library databases with predefined search strategies. The reference lists of identified papers were reviewed for additional studies. The entire procedure adopted in the bibliographic search for the original contributions is shown in Appendix 2.

The quality of the scientific evidence and the consequent weight of the recommendations were assessed using the *American Academy of Neurology* (AAN) Manual [27]. According to the AAN parameters, the quality of each scientific contribution is divided into four classes: the highest (class I) comprises the most robust methodological studies and the lowest (class IV) clinical case studies and *case reports*. The weight of the resulting recommendations varies from defined (level A) to probable (level B), possible (level C), or cannot be calculated because of absent or conflicting information (level U).

The critical review of the literature was carried out by members of the BTE study group selected on the basis of their skills. Each question was assigned to a pair of reviewers who received a list of abstracts identified by the systematic review of the literature. Each pair had the following functions:

- Independent examination of the abstracts and exclusion of those deemed nonpertinent (topic not addressing the question, publication only as an abstract, narrative review, case report) and those in a language other than English.
- Discussion of the contributions on which their opinion differed, to reach a consensus.
- Independent examination of the eligible works in full and assignment to the class corresponding to the most appropriate qualitative level; in case of disagreement, the contribution was discussed to achieve consensus.

- Joint formulation of the recommendation.

Each pair was asked to provide a brief summary of their work, including the selection of the contributions deemed suitable for assessment and, where indicated, presentation of the main results and the formulation of the recommendations.

Where necessary, the questions were aggregated on the basis of common themes or domains. The selection of the contributions identified by the bibliographical research by the reviewers is illustrated in Appendix 3 where the studies are tabulated and the references used for the recommendations are inserted. Only the contributions supporting the recommendations are given here.

Results

A total of 7827 unique records were retrieved which were screened in title/abstract or full text for inclusion. The flowchart of the included and excluded papers is reported in Fig. 1. A total of 7285 studies were excluded as not pertinent letters or case reports. A total of 542 full papers were screened, and 400 were excluded because they included small samples, overlapped with other included studies, were not strictly pertinent with the panel aims, or were letters. Thus, 142 studies constituted the core literature for the consensus. All these papers are cited in the answers to specific questions and are listed in Appendix 3.

For each question, Table 1 summarizes the questions (and related subquestions), the references with ratings, and one or more synthetic answers representing the summary of the existing literature with the related level of evidence.

Discussion

From the analysis of the recommendations resulting from the 17 questions, some areas of particular importance emerged. First, epilepsy in BT represents more than a simple symptom.

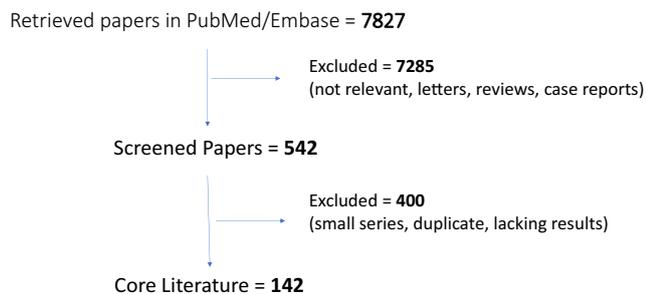


Fig. 1 Flowchart of the included and excluded studies

The panel underlines that for all BT there is no evidence of relation between occurrence of seizure and recurrence or aggravation of the tumor, except for seizure-free patients with glioblastoma in which recurrence of seizures is associated with tumor recurrence. There is no evidence that histological type or localization of the BT affects the response to an antiepileptic drug. An important issue is related to the choice of the drug and to its possible effects on survival. Although class III studies showed a favorable effect on survival of valproate or levetiracetam in combination with chemo- and radiotherapy, a single meta-analysis showed that antiepileptic drugs have no effect on survival. The panel thus evidenced conflicting data on this topic. Finally, there is no robust evidence to link the choice of an antiepileptic drug to a specific biomarker, including genetic indexes IDH1, MGMT, and LOH 1p LOH19.

Another important issue is related to the role of the electroencephalogram (EEG) as indicator for AED treatment. To date, the literature does not provide sufficient evidence to make recommendations on the need for periodic EEGs in patients with BT treated with antiepileptic drugs. Only in patients with temporal lobe ganglioglioma the panel was able to recommend that periodic EEG should not be considered. Also in patients with BT without seizures but with epileptiform abnormalities, there are no data supporting the use of antiepileptic drugs. Regarding the role of EEG during the perioperative period, the literature does not provide sufficient evidence to make recommendations on the need for periodic EEGs; the EEG may be considered only in patients with meningiomas and only in the immediate perioperative period.

Overall, to date, literature data are lacking and impeding recommendations about use and best timing of EEG in BTE patients, concerning monitoring of antiepileptic therapy, perisurgical or postsurgical timing, or histological type. Highly consistent data refer only to meningioma patients, for whom the EEG might be considered in the immediate postoperative period, and to temporal lobe ganglioglioma patients treated with antiepileptic drugs, for whom periodic EEG should not be considered.

Regarding the role of antiepileptic prophylaxis in BT patients, there is robust evidence that both short-term and long-term prophylaxes are not recommended and that can be gradually discontinued after removal of the tumor. Also, in patients with brain metastases, antiepileptic drugs have not proven effective in preventing seizures; therefore, no drug should be considered for prophylaxis, even if patients underwent neurosurgery or gamma knife treatment.

Regarding when to start AED therapy, the panel evidenced that antiepileptic therapy is indicated after a first seizure in patients with a BT. This choice is not different from the ILAE recommendations [30, 127] on the treatment of first seizures in nononcological epileptic population.

Table 1 Questions addressing the major diagnostic and therapeutic problems about BTE identified by board members, with chosen literature, related rating and answer with level of evidence

Question	Answer	Level of evidence	Reference	Rating
1 Eeg as marker for antiepileptic treatment				
A. Should an EEG be done in a patient with brain tumors without epileptic seizures?	In patients with meningioma, the EEG may be considered in the immediate postoperative period.	C	Radhakrishnan A et al., 2006 [111] Wirsching HG et al., 2016 [152]	III III
	Literature data do not provide sufficient evidence for meningiomas after the postoperative phase and for all other brain tumors.	U		
B. In patients with brain tumors without seizures and no epileptiform EEG abnormalities, are epileptic drugs necessary?	In the absence of relevant studies, reviewers are unable to make specific recommendation.	U	Radhakrishnan A et al., 2006 [111] Wirsching HG et al., 2016 [152]	III III
C. In patients with brain tumors without seizures but with epileptiform EEG abnormalities, are antiepileptic drugs necessary?	The literature does not provide evidence for antiepileptic drug treatment in patients with brain tumors without seizures but with epileptiform EEG abnormalities. The reviewers recommend future studies.	U	Radhakrishnan A et al., 2006 [111] Wirsching HG et al., 2016 [152]	III III
D. Are periodic EEG required in patients receiving antiepileptic treatment?	Periodic EEG should not be considered in patients receiving antiepileptic treatment because of BTE due to temporal lobe ganglioglioma.	C	Radhakrishnan A et al., 2006 [111] Wirsching HG et al., 2016 [152]	III III
	The literature does not provide sufficient evidence to make recommendations on the need for periodic EEGs in patients with other brain tumors treated with antiepileptic drugs. The reviewers recommend future studies in order to define the indication and the best timing of the EEG in patients with BTE.	U		
2 Epileptic seizures and tumor relapse				
Can a seizure be an earlier indicator of tumor relapse than radiological findings?	Recurrence of seizures should be considered as tumor relapse in patients with glioblastoma who have complete postoperative control of epileptic seizures.	B	Roelcke U, Wyss MT et al., 2016 [118] Levy G, Lervat C, et al., 2016 [75]	III III III
	For all other brain tumors there is no evidence of relation between seizure and tumor relapse or aggravation.	U	Kerkhof M, Koekkoek JAF et al., 2016 [55] Toledo M, Sarria-Estrada S et al., 2015 [138] Tandon PN, Mahapatra AK et al., 2001 [135] Chaichana KL, Parker SL et al., 2009 [20] Di Bonaventura C, Albini M et al., 2017 [26]	III II III
3 Antiepileptic prophylaxis in patients with brain tumor				
A. In patients with brain tumors without a seizure, can prophylaxis with antiepileptic drugs be indicated to prevent epileptic seizures?	In the patient with brain tumor without seizures, both short-term and long-term prophylaxis should not be recommended.	B	Spena G, Schucht P et al., 2017 [132] Wu AS, Trinh VT et al., 2013 [153]	IV IV IV
B. In patients under prophylactic antiepileptic treatment, can the therapy be suspended after removal of the tumor?	Physicians should consider gradual withdrawal of the prophylactic antiepileptic treatment.	B	Komotar RJ, Raper DM et al., 2011 [65] Sughrue ME, Rutkowski MJ et al., 2011 [134]	IV III IV IV

Table 1 (continued)

Question	Answer	Level of evidence	Reference	Rating
			Lwu S, Hamilton MG et al., 2010 [81]	III
			Lockney DT, Vaziri S et al., 2017 [79]	II
			Islim A, McKeever IS et al., 2017 [48]	II
			Lapointe S, Florescu M, et al., 2015 [72]	IV
			Ansari SF, Bohnstedt BN et al., 2014 [2]	II
			Wychowski T, Wang H et al. 2013 [154]	II
			Garbossa D, Panciani PP et al. 2013 [34]	II
			Rosati A, Tomassini A et al., 2009 [119]	II
			Kong X, Guan J et al., 2015 [66]	II
			Sayegh ET, Fakurnejad S et al., 2014 [126]	II
			Perry J, Zinman L et al., 2006 [104]	II
			Liang S, Zhang J et al., 2016 [76]	II
			Glantz MJ, Cole BF et al., 2000 [37]	II
			Tremont-Lukats IW, Ratilal BO et al., 2008 [140]	II
			Lobos-Urbina D, Kittsteiner-Manubens L et al., 2017 [78]	II
			Sirven JI, Wingerchuk DM et al., 2004 [129]	II
4	treatment of the first epileptic seizure			
	Can antiepileptic treatment be used to control recurrences of seizures in patients with a first seizure due to brain tumor?	Antiepileptic therapy is indicated after a first seizure in a patient with a brain tumor.	A	
			Glantz M, 2000 [37]	II
			Krumholz A, 2015 [68]	I
			Berg AT, 2008 [11]	I
			Annegers JK, 1986 [1]	II
			Jallon P, 2001 [51]	III
5	Location of the brain tumor and therapeutic choice			
	Can the location of the tumor influence the choice of the antiepileptic drug?	The choice of the drug is not determined by the location of the tumor.	A	
			Chang EF, 2008 [22]	III
			Sirven J, 2004 [129]	I
			Das RR, 2012 [24]	III
			Hardesty DA, 2011 [46]	III
			Wychowsky TH, 2013	III
			Spena G, 2017 [132]	III
6	Molecular markers and indexes			
		There are no studies linking the choice of the drug to specific molecular indices.	U	
			Skardelly M et al., 2015 [130]	IV
				IV

Table 1 (continued)

Question	Answer	Level of evidence	Reference	Rating
Can the presence of certain genetic indexes (IDH1, MGMT, LOH 1p LOH19) influence the antiepileptic drug choice?	The reviewers recommend future studies to understand whether at least IDH1/IDH2 mutations may influence the antiepileptic choice.		Gonen T et al., 2014 [40]	
7/8 Choice of antiepileptic drug and severity of brain tumor (who grades I-II-III)				
A. In the patient with a WHO grade I /II /III brain tumor for whom antiepileptic treatment is indicated, what is the drug of first choice?	There are no data for all the subquestions, so no specific drugs can be recommended for particular type of tumor, regardless of its course.	U	Kerrigan S, Grant R, 2011 [56]	IV
B. What is the drug of first choice during disease stability and progression or relapse?	Nonetheless, the reviewers suggest to avoid enzyme-inducing antiepileptic drugs because of their interference with antitumoral drugs.		Yuan Y et al., 2014 [157, 158]	IV
C. What is the drug of first choice in the presence of a meningioma?	The reviewers suggest the need for high-quality randomized trials comparing the efficacy and tolerability of antiepileptic drugs in patients with BTE due to WHO grade I-II-III BT.		Nasr ZG, Paravattil B, Wilby KJ, 2016 [28]	II
			Yuan Y et al., 2015 [159]	III
			Rossetti AO et al., 2014 [121]	III
			Lim DA et al., 2009 [77]	IV
			Merrel RT et al., 2010 [95]	III
			Maschio M et al., 2017 [93]	III
			Maschio M et al., 2008 [83]	III
			Maschio M et al., 2011 [86]	III
			Maschio M et al., 2011 [87]	IV
			Maschio M et al., 2012 [88]	
			Maschio M et al., 2012 [89]	
			Maschio M et al., 2017 [92]	
			Maschio M et al., 2017 [94]	
			Striano S et al., 2002 [133]	
			Rudà R et al., 2018 [123]	
			Newton HB et al., 2006 [99]	
			Rosati A et al., 2010 [120]	
			Villanueva V et al., 2016 [145]	
			Vecht CA et al., 2017 [144]	
9 Choice of antiepileptic drug and high-grade brain tumor (who grade IV)				
A. In the patient with a WHO grade IV brain tumor for whom antiepileptic treatment is indicated, what is the drug of first choice?	There are no data for all the subquestions so no specific drug can be recommended for any type of tumor regardless of its the course.	U	Tinchon A, Oberdorfer S et al., 2015 [137]	IV
B. What is the drug of choice in the phase of stable disease or in progression or relapse?	Nonetheless, the reviewers suggest to avoid enzyme-inducing antiepileptic drugs because of their interference with antitumoral drugs.		Kerkhof M, Dielemans JC et al., 2013 [54]	IV
	The reviewers suggest the need for randomized quality trials comparing the efficacy and tolerability of antiepileptic drugs in patients with BTE due to WHO grade IV BT.		Saria MG, Corle C et al., 2013 [125]	IV
			Maschio M, Dinapoli L et al., 2008 [83]	IV

Table 1 (continued)

Question	Answer	Level of evidence	Reference	Rating
			Maschio M, Dinapoli L et al., 2011 [86]	IV
			Maschio M, Dinapoli L et al., 2011 [87]	IV
			Maschio M, Dinapoli L et al., 2012 [89]	III
			Maschio M, Dinapoli L et al., 2012 [89]	IV
			Bähr O, Hermisson M, et al., 2012 [6]	IV
			Usery JB, Michael LM 2nd et al., 2010 [141]	IV
			Rosati A, Buttolo L et al., 2010 [120]	IV
			Novy J, Stupp R et al. 2009 [100]	IV
			Wagner G, Wilms E et al., 2003 [147]	IV
			Perry JR, Sawka C, 1996 [103]	IV
			Rossetti AO, Jeckelmann S et al., 2014 [122]	IV
			Sepúlveda-Sánchez JM, Conde-Moreno A et al., 2017 [128]	IV
			Vecht C, Duran-Peña A et al. 2017 [144]	IV
10 Cerebral metastasis				
A. Is antiepileptic treatment indicated in the patient with brain metastases without seizures?	Antiepileptic drugs have not proven effective in preventing seizures in patients with brain metastasis.	B	Glantz et al., 1996 [36]	I
	No drugs should be considered for prophylaxis in patients with brain metastases without a seizure.		Forsyth et al., 2003 [32]	III
			Byrne et al., 1983 [18]	III
B. Is antiepileptic treatment necessary in the post-operative period?	For patients with brain metastases who underwent neurosurgery or gamma-knife treatment, pharmacological prophylaxis did not reduce the incidence of seizures in the post-operative period; the weight of the adverse effects of enzyme-inducing drugs may be emphasized.	C	Wu AS, 2013 [3]	IV
	No prophylactic antiepileptic treatment should be used in patients with brain metastases without post-operative seizures.	B	Zachenhofer, 2011 [160]	IV
			Gokhale, 2013 [38]	IV
			Ansari SF, 2014 [2]	III
			Lee MH, 2013 [73]	IV
C. When treatment is indicated, which drug is first choice?	There is not enough evidence to suggest any one drug of first choice in patients in whom treatment is indicated.	U	Maschio M et al., 2010 [85]	IV
			Newton HB et al., 2006 [99]	IV
			Newton HB et al., 2007	IV
			Maschio M et al., 2008 [83]	IV
			Maschio M et al., 2009 [84]	IV
			Sepúlveda-Sánchez JM et al., 2017 [128]	IV
			Toledo M et al., 2017	IV
			Bedetti C et al., 2017 [8]	IV
11 Do antiepileptic drugs have any effect on the survival of patients with bte?		U	Arik Y et al., 2014 [3]	II
				III

Table 1 (continued)

Question	Answer	Level of evidence	Reference	Rating
B. Can neuropsychiatric evaluation be useful in the choice of the antiepileptic drug in BTE-patients?	Neuropsychiatric evaluation may be considered when choosing anti-epileptic drugs in BTE-patients.	C	Belcastro V et al., 2017 [9]	III II
C. Can neuropsychological evaluation be useful to monitor the side effects of antiepileptic treatment in BTE-patients?	Neuropsychological evaluation should be considered to monitor side effects of antiepileptic treatment in BTE-patients.	B	Bosma I et al., 2007 [16]	II IV
D. Should antiepileptic treatment be indicated for its effects on premorbid functional disability and QoL?	Antiepileptic treatment should be chosen on the basis of knowledge of its effects on premorbid functional disability. The choice of adequate therapy and consequently reduction of the seizures, has positive effects on the quality of life perceived by the patient.	B	de Groot M et al., 2013 [25]	IV IV
			Klein M et al., 2002 [59]	III IV
			Klein M et al., 2003 [60]	III II
			Maschio M et al., 2011 [86]	III III
			Maschio M et al., 2012 [88]	IV
			Maschio M et al., 2012 [89]	
			Maschio M et al., 2014 [90]	
			Maschio M et al., 2017 [92]	
			Maschio M et al., 2017 [93]	
			Rahman Z et al., 2015 [113]	
			Tanti MJ et al., 2017 [136]	
			Waagemans M et al., 2011 [146]	
			Yavas C et al., 2011 [156]	
17 Does the choice of an antiepileptic drug consider possible interactions with antitumoral therapies? if so, what drugs are to be preferred?				
	In BTE-patients receiving chemotherapy, the choice of an antiepileptic drug should consider possible interactions with antitumor therapies, since antiepileptic drugs can reduce plasma levels of oncological drugs and increase the risk of toxicity of both treatments.	B	Gilbert MR et al., 2003 [35]	III III
			Bourg V et al., 2001 [17]	III III
			Berg AK et al., 2016 [12]	III III
	In choosing the antiepileptic drug, enzyme inducers (carbamazepine, phenytoin, phenobarbital) should not be considered.	B	Kuhn JG et al., 2007 [70]	III III
			Loghini ME et al., 2007 [80]	III III
	Among the newer generation drugs, levetiracetam, lamotrigine and topiramate should be considered as first choice.	B	Weller M et al., 2011 [149]	III III
	Valproic acid should also be considered as a first-choice drug.	B	Grossman SA et al., 1998 [42]	III III
			Phuphanich S et al., 2005 [107]	II III
			Smith DA et al., 2009 [131]	III III
			Gilbert MR, 2003 [35]	III III
			Wen PY et al., 2006 [150]	II III
			Prados MD et al., 2006 [108]	III III
			Grossman SA et al., 2008 [41]	III III
			Santisteban M et al., 2009 [124]	III III
			Pursche et al., 2008 [110]	III II

Table 1 (continued)

Question	Answer	Level of evidence	Reference	Rating
			Iuchi T et al., 2015 [49]	
			Reeves D et al., 2016 [115]	
			Riva M et al., 2000 [116]	
			Chalk JB et al., 1984 [21]	
			Oberndorfer S et al., 2005 [101]	
			Bacher CA et al., 2013	
			Yat-Ming Woo P et al., 2015 [155]	
			Kim YH et al., 2015 [58]	
			Knudsen-Baas K et al., 2016 [61]	
			Tinchon A et al., 2015 [137]	
			Rodman JH et al., 1994 [117]	
			Innocenti F et al., 2004 [47]	
			Mross K et al., 1994 [97]	
			Kuhn JG et al., 2002 [69]	

There are no data to recommend specific drugs for particular type of tumor, regardless of its course. Nonetheless, the reviewers suggest to avoid enzyme-inducing antiepileptic drugs because of their interference with antitumoral drugs. There is no evidence to recommend a specific antiepileptic drug in BTE patients who failed to respond to a first antiepileptic treatment. Given the low quality of the studies and the conflicting results, it is not possible to confirm the superiority of any therapeutic strategy over the other (alternative monotherapy vs. polytherapy). The reviewers suggest the need for high-quality randomized trials comparing the efficacy and tolerability of antiepileptic drugs in patients with BTE.

Due to the fact that adverse treatment effects have a heavy impact on the quality of life of these patients, neuropsychological and neuropsychiatric evaluation may be considered in choosing the most appropriate drug, but monitoring of adverse treatment effects during follow-up, it should be considered. In fact, the choice of adequate therapy and the consequent reduction of the seizures has positive effects on the quality of life perceived by the patient.

A fundamental issue addressed by the panel is that, in patients receiving chemotherapy, the choice of the antiepileptic drug should consider possible interactions with antitumor therapies, since antiepileptic drugs can reduce plasma levels

of oncological drugs and increase the risk of toxicity of both treatments. For this reason, enzyme inducers (carbamazepine, phenytoin, phenobarbital) should not be considered. The newer generation drugs should be considered as first choice and among them are levetiracetam, lamotrigine, and topiramate. Valproic acid should also be considered.

In adults with BTE, after removal of the brain tumor or with a stable brain tumor who are seizure-free for at least 2 years, there are no data sustaining a discontinuation of antiepileptic drugs. The reviewers recommend future studies on this issue, given the importance of the subject and the heterogeneous data available to date. At the same time, withdrawal of antiepileptic drugs should not be considered in BTE patients with progression or recurrence of their brain tumor, even if seizure-free for at least 2 years.

Conclusion

Patients with BRE present a complex therapeutic profile and require a unique and multidisciplinary approach. BRE results in a real challenge from many points of view—therapeutic, support, and psychosocial—due to the presence of two pathologies: on the one hand, the BT, and on the other hand,

epilepsy. A diagnosis of BT as well as just the idea of cancer alone, in most patients, is enough to cause deep difficulties: behavioral, emotional, and intellectual. These problems can have negative effects on daily life activities and impair the ability to lead an independent life. Patient management requires careful consideration of many factors by clinicians.

To date, this consensus statement represents a synthesis of the best available evidence on BTE management. The panel reached complete agreement on each of the questions and the main topics; thus, this document fully expresses the opinion of Italian experts in this field.

The contribution of different professional roles and of patients' representatives has allowed recommendations to be formulated that cover problems related to common clinical practice. The work of this panel has highlighted the need for studies with robust design in the field of BTE management, which are crucial to standardize clinical practice and, at the same time, to take care of the quality of life of persons with BTE. Finally, a well-structured multidisciplinary team approach is essential in managing these patients with dual pathology, with specialists from different areas addressing all aspects of the patient's life.

Compliance with ethical standards

Conflict of interest Dr. Marta Maschio has received support to travel to congresses from Eisai Srl, has participated in scientific advisory boards for Eisai Srl, has participated in pharmaceutical industry sponsored symposia for UCB Pharma, and has received research grants from UCB Pharma. Dr. Angela La Neve has received speaker's or consultancy fees from Eisai Srl, Mylan, Sanofi-Aventis, and UCB Pharma. Dr. Gaetano Zaccara has received speaker's or consultancy fees from Eisai Srl, Sanofi-Aventis, and UCB Pharma. Dr. Cinzia Costa has received speaker's or consultancy fees from Eisai Srl, FIDIA, Mylan, and UCB. Dr. Filippo Dainese has received speaker's or consultancy fees from Eisai and UCB Pharma. Dr. Umberto Aguglia has received research grants from Biogen. Dr. Ettore Beghi has received grants from UCB Pharma and grants from Italian Ministry of Health. Dr. Federica Ranzato has participated in hospital meetings and sponsored symposia from UCB Pharma and Eisai Srl.00. The other authors declare that they have no conflict of interest.

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