Epilepsy and insular Grade II gliomas: an interdisciplinary point of view from a retrospective monocentric series of 46 cases

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Object. There are few data in the literature concerning a multimodal approach to insular WHO Grade II gliomas (GIIGs) and the control of epilepsy after treatment. In this paper, the authors describe a monocentric series of 46 cases in which patients underwent various sequential treatments for insular GIIGs. On the basis of global results with regard to epilepsy, the respective interests in the various treatments are discussed.

Methods. Available data on 46 patients harboring insular GIIGs were extracted from a local database of 288 GIIGs. The various therapeutic sequences were analyzed in parallel with the course of seizure frequency.

Results. Despite the usual difficulties with seizure quantification in retrospective studies, the authors showed that 1) the negative course of seizure frequency was mostly connected to tumor progression, 2) surgery almost always had a favorable effect on epilepsy, and 3) chemotherapy had a mostly favorable effect with acceptable tolerance. The authors were unable to draw conclusions about the role of radiotherapy given the too few cases.

Conclusions. This extensive experience with insular GIIGs tends to confirm interest in their surgical removal and supports interest in chemotherapy from an epileptological point of view. (DOI: 10.3171/2009.6.FOCUS09102)

KEY WORDS • World Health Organization Grade II glioma • chemotherapy • low-grade glioma • insula • seizure • epilepsy • surgery

EPILEPSY is a common complication in patients with primary brain tumors.^{39,40,77,78} Gliomas represent the majority of primitive tumors of the brain, with GIIGs making up ~ 15%;⁴ insular gliomas make up 15% of the WHO Grade II lesions (Réseau d'Etude des Gliomes databank).

The category of GIIGs is one of the most epileptogenic tumor groups; that is, it is the main symptom in up to 80% of patients with GIIGs. Intractable forms of epilepsy are observed in ~ 10 to 20% of cases.^{3,6,7,11,16,21,32,33,48,53,54,57,63,79,85} The precise mechanisms involved in the etiology of epilepsy remain globally unknown,^{33,37,44,64} and treatment strategies are still matters for discussion.

Surgery is probably one of the domains with the most development in the last few years. The approach is nevertheless technically difficult and reserved for specialized teams. Recent series have been rare.^{22,23,27,45,59,66,69,76,84,86} Furthermore, there is no consensus regarding the optimal type of surgery, for example, lesionectomy alone or

lesionectomy combined with the removal of surrounding epileptogenic cortex. The majority of concerned teams have reported favorable epileptological results in ~ 80% of cases with or without the removal of mesiotemporal structures.^{66,70,84,86}

Data concerning radiotherapy are exceptional.⁶⁸ Moreover, to our knowledge, there are no specific data regarding the impact of chemotherapy or combining the strategies of surgery and chemotherapy in the control of epilepsy.

We here present a retrospective study undertaken at one French center engaged in the Réseau d'Etude des Gliomes (Glioma Study Network). We estimated the rate of seizures in a series of 46 patients with insular GIIGs and the effect of combined treatments on epilepsy.

Methods

We retrospectively reviewed available data in all cases of insular GIIGs in adults from a database at the university hospital in Nancy, France, containing 288 patients with WHO GIIGs. The insular glioma location was categorized using the classification of Yaşargil et al.⁸⁴ According to this scheme, Type 3 tumors are restricted to

Abbreviations used in this paper: AED = antiepilepsy drug; BI = bevacizumab + irinotecan; GIIG = WHO Grade II glioma; PCV = procarbazine + lomustine (CCNU) + vincristine; TMZ = temozolomide; WS = wait and see.

TABLE 1: Summary of initial data in 22 patients who did not undergo surgery*

Case No.	Age at Diagnosis (yrs), Sex	1st Symptoms & Signs	Seizures at Base-line	Side	Yaşargil Classification	WHO Tumor Type	AED†
1	27, F	headache, deficit	—	lt	5B	All	—
2	59, M	seizure, MCI	O	lt	5B	—	1) Lev
3	37, F	headache, MCI	—	rt	5B	—	1) Lev; 2) Val
4	38, M	seizure	M	lt	5B	—	1) Oxcar; 2) Oxcar + Lev
5	46, F	seizure	W	rt	5B	—	1) Gaba; 2) Gaba + Lev; 3) Lev + Prega
6	48, M	seizure, MCI	O	lt	3A	OII	1) Lev
7	41, M	seizure	M	rt	3B	OII	1) Lev
8	42, M	seizure	O	lt	5B	OII	1) Val; 2) no AEDs; 2) Oxcar
9	36, F	seizure	W	lt	5B	OII	1) Oxcar; 2) Oxcar + Topir; 3) Topir + Lev; 4) Lev + Lamo
10	56, M	seizure	M	rt	3B	OII	1) Lev
11	34, F	headache, seizure	M	rt	5B	—	1) Lev
12	31, F	seizure, MCI	M	lt	5B	—	1) Lev
13	44, M	seizure	W	lt	5B	—	1) Lev
14	48, M	seizure	M	lt	5B	OII	1) Lev; 2) Lev + Prega
15	42, M	seizure	M	lt	5B	OII	1) Oxcar; 2) Val; 3) Lev; 4) Lev + Topir; 5) Lev + Topir + Lamo
16	35, M	seizure	O	lt	5B	OII	1) Val; 2) Carba; 3) Carba + Topir
17	36, M	seizure	O	lt	5A	OII	1) Lamo
18	57, F	seizure	M	rt	5B	All	1) barbiturates; 2) Carba; 3) no AEDs; 4) Carba
19	58, F	seizure	D	lt	5B	All	1) Gaba; 2) Topir; 3) Topir + Lev
20	47, M	seizure	D	lt	5B	All	1) Carba; 2) Carba + vigabatrin; 3) Carba
21	37, M	seizure	D	lt	5B	OII	1) Val; 2) Carba; 3) Lev; 4) Lev + Prega
22	45, M	seizure	M	lt	5B	OII	1) Oxcar; 2) Lev; 3) Lev + Oxcar

* All = astrocytoma Type II; Carba = carbamazepine; D = daily; Gaba = gabapentin; Lamo = lamotrigine; Lev = levetiracetam; M = monthly; MCI = mild cognitive impairment; O = occasionally; OII = oligodendroglioma Type II; Oxcar = oxcarbazepine; Prega = pregabalin; Topir = topiramate; Val = valproate; W = weekly; — = not applicable.

† Numbering corresponds to the succession of therapeutic sequences.

the insula or parts of it (Type 3A) or may include the corresponding opercula (Type 3B). In addition to the insula and opercula, Type 5 tumors involve 1 or both paralimbic orbitofrontal and temporopolar areas, either without (Type 5A) or with (Type 5B) parts of the limbic system.

Baseline quantification of epilepsy was predicated on a simple classification distributing seizures into 4 categories as transcribed in our database: daily, weekly, monthly, or occasional. The evolution of seizure frequency was categorized using the Engel criteria:²⁸ EI = seizure free or auras only, EII = infrequent seizures, EIII = worthwhile improvement in seizure frequency or severity, and EIV = no significant improvement.

Results

Forty-six of 288 GIIIG cases were included in our analysis. Twenty-four patients benefited from a surgical procedure, and 22 did not undergo surgery. The epileptological and treatment characteristics of the 46 patients are summarized in Tables 1–4. Data concerning chemotherapy are summarized in Table 5.

Nonsurgical Population

Clinical Data. The patients who did not undergo surgery consisted of 14 men and 8 women, ranging in age from 27–59 years (mean 42 years). Sixteen gliomas involved the dominant left hemisphere and 6 the nondominant right side. Three patients reported intense headaches; and 4, mild cognitive impairment. All but 1 (light paresis) preoperative neurological examination were normal.

Radiological Data. Pretherapeutic MR imaging revealed, according to the classification of Yaşargil et al.,⁸⁴ the following glioma locations: 1 patient, Type 3A; 2 patients, Type 3B; 1 patient, Type 5A; and 18 patients, Type 5B.

Neuropathological Data. The neuropathological examination led to the diagnosis of 4 WHO Grade II astrocytomas and 11 WHO Grade II oligodendrogliomas. Seven patients had no neuropathological confirmation of their lesions (noncontributive biopsy findings or no biopsy procedure because of the initial WS period).

Oncological Strategies. From an oncological point of

TABLE 2: Seizure evolution in 22 patients who did not undergo surgery*

Case No.	1st Tx†	Seizure Grade After 1st Tx‡	2nd Tx†	Seizure Grade After 2nd Tx‡	3rd Tx	Seizure Grade After 3rd Tx‡	4th Tx†	Seizure Grade After 4th Tx‡	FU
1	TMZ × 15	EI	PCV × 4	—	WS	—	—	—	—
2	WS	EIII	TMZ × 9	EIII→EI	—	—	—	—	—
3	WS	EI	—	—	—	—	—	—	—
4	WS	EIV	TMZ × 12	EIV→EII	WS	EII→EIII	—	—	—
5	WS	EII	—	—	—	—	—	—	—
6	TMZ × 12	EI	WS	EI	—	—	—	—	—
7	TMZ × 14	EII	—	—	—	—	—	—	—
8	RT	EI	TMZ × 21	EI	WS	EI→EII	—	—	—
9	WS	EI	TMZ × 12	EI	RT	EI	PCV × 2	—	CE 16 × 8, current: WS
10	TMZ	EI	AT during course w/ BI	EI	—	—	—	—	fast AT, BI w/out effect, RT, death
11	WS	EIII	—	—	—	—	—	—	—
12	WS	EIII	—	—	—	—	—	—	—
13	WS	EI	—	—	—	—	—	—	—
14	WS	EIV	TMZ × 4	EIII	—	—	—	—	current: TMZ
15	WS	EIII	PCV × 4	EIII	WS	EIII→EIV	TMZ × 7	EIII	current: TMZ
16	WS	EIII	F × 14	EIII→EIV	RT	—	—	—	RT in discussion
17	WS	EII	TMZ × 9	EII	AT during PC	EI	—	—	fast AT, death
18	WS	EIV	PCV × 6	EI	WS	EIV	TMZ × 12	EI	AT during WS, F, PC, & death
19	WS	EIV	TMZ × 16	EI	WS	EIV	TMZ × 6→AT	EII	RT, F, CE, PC, & death
20	WS	EIV	PCV × 4	EII	WS	EIV	AT→RT	EII	WS, TMZ, CE, PC, & death
21	WS	EIV	TMZ × 24	EIII	WS	EIV	F	EIV	AT during course w/ CE, RT, PC, & death
22	WS	EIV	TMZ × 24	EII	RT	death from intratumoral bleeding	—	—	—

* AT = anaplastic transformation; CE = carboplatin + etoposide; F = fotemustine; FU = follow-up; PC = palliative care; RT = radiotherapy.

† Number of cycles of chemotherapy indicated by the number following the multiplication sign.

‡ Engel classification: EI = seizure free; EII = occasional seizures; EIII = improvement in seizures but remain present; EIV = no modification or escalation in seizures.

view, various strategies were considered. Among the first-line strategies were 17 cases of close monitoring (WS), 4 cases of TMZ-based chemotherapy, and 1 case of radiotherapy. Among the second-line strategies were 1 case of WS, 9 TMZ-based chemotherapy, 4 PCV-based chemotherapy, 1 fotemustine-based chemotherapy, and 1 BI-based chemotherapy; among the third-line strategies were noted 7 cases of WS and 3 cases of radiotherapy; and among the fourth-line strategies were 3 cases of TMZ-, 1 PCV-, and 1 fotemustine-based chemotherapeutic treatments and 1 case of radiotherapy treatment.

Epilepsy. Seizure(s) was the first symptom in 20 of 22 cases. During the initial period, according to our database

classification, seizure frequency was considered as occasionally (5 cases), monthly (9 cases), weekly (3 cases), and daily (3 cases). During the course of their epileptic disease, 8 patients were treated with 1 AED, 7 with 2 AEDs, 3 with 3 AEDs, 2 with 4 AEDs, and 1 with 5 AEDs. On the whole, 11 patients were treated with monotherapy and 10 with polytherapy.

The control of epilepsy differed according to the various treatment strategies. After close monitoring as the first-line strategy, the condition of ~ 30% of the patients improved considerably with AED treatment only (EI: 3 patients, EII: 2 patients) and improved modestly, stabilized, or deteriorated in ~ 70% despite the AEDs (EIII: 5 patients, EIV: 7 patients). After TMZ-based chemother-

TABLE 3: Summary of pretreatment data in 24 patients who underwent surgery*

Case No.	Age at Diagnosis (yrs), Sex	1st Symptoms & Signs	Seizures at Baseline	Side	Yaşargil Classification	WHO Tumor Type	AED
S1	40, F	headache	—	rt	3B	OII (biopsy), OIII (late surgery)	—
S2	53, M	seizure	M	lt	3B	OII	1) Gaba
S3	63, M	seizure	O	rt	3B	OAll	1) Val; 2) Lamo
S4	41, M	seizure	M then W	lt	5B	OII	1) Val; 2) Oxcar; 3) Oxcar + Lev; 4) Lev + Topir
S5	33, M	seizure	W	lt	2B	OII	1) Oxcar; 2) Oxcar + Lev; 3) Oxcar + Lamo; 4) Lamo + Lev; 5) Lamo
S6	29, F	seizure	M	lt	5B	OII (biopsy), OAll (late surgery)	1) Lev; 2) Lev + Lamo; 3) Lev + Lamo + Carba; 4) Lev + Lamo; 5) Lamo + Zonis; 6) Lev + Zonis
S7	29, F	seizure	O	rt	5B	OII	1) Topir
S8	22, M	seizure	M	lt	5B	OII (biopsy), OII (surgery)	1) Oxcar; 2) Lev
S9	43, M	seizure	M	lt	5A	OII	1) Oxcar; 2) Lev; 3) Lev + Pregab; 4) Lev + Lamo
S10	56, M	seizure	O	lt	5B	OII	1) Lev
S11	35, F	seizure	M	lt	5B	OII (S1), OII (S2)	1) Lev
S12	25, F	seizure	D	rt	5B	OAll	1) Lamo; 2) Lamo + Lev; 3) Lamo + Zonis
S13	39, F	seizure	O	rt	5B	OII	1) Oxcar
S14	37, M	seizure	O	rt	5A	OII	1) Lev
S15	54, M	seizure	O	rt	5B	OII	1) Val
S16	73, M	seizure	M	lt	5B	OII	1) Lev
S17	33, M	seizure	M	rt	5B	All (biopsy), OII (surgery)	1) Carba; 2) Carba + Lev; 3) Carba + Topir
S18	57, F	seizure	O	rt	5A	OII	1) Gaba; 2) Lev; 3) Lev + Zonis
S19	38, M	seizure	O	lt	5A	OII	1) Oxcar
S20	26, F	seizure	O	lt	5B	OII	1) Carba; 1) Carba + Topir
S21	17, M	seizure	O	lt	5A	OII	1) Lev; 2) Lev + Topir
S22	34, F	seizure	O	rt	5A	OII	1) Carba; 2) Carba + Topir; 3) Topir; 4) †AE; 5) Lamo
S23	36, F	seizure	W	rt	5B	OII	1) Topir
S24	29, M	seizure	M	rt	3B	OII	1) Val; 2) Carba

* †AE = AED stopped; biopsy = biopsy procedure first performed and then surgery; late surgery = surgery was performed after anaplastic transformation; OAll = oligoastrocytoma Type II; OAlll = oligoastrocytoma Type III; OIII = oligodendroglioma Type III; S1 = first surgery; S2 = second surgery; Zonis = zonisamide.

apy as the first-line strategy, all of the patients improved (EI: 3 patients, EII: 1 patient).

After a chemotherapy-based second-line strategy (9 TMZ-based, 4 PCV-based, 1 fotemustine-based, and 1 BI-based case), 10 patients (90%) improved (6 patients gained 2 Engel classes and 4 patients gained 1 Engel class) and 1 stabilized. Three patients remained seizure free before and after the chemotherapy treatment.

The number of patients is too limited to report the results of radiotherapy as well as for the third and fourth lines of treatment.

Surgical Population

Clinical Data. The 24 patients who underwent surgery consisted of 14 men and 10 women, ranging in age from 17 to 73 years (mean 39 years). Twelve gliomas involved the dominant left hemisphere and 12 the nondom-

inant right side. One patient reported intense headache, and none reported cognitive impairment. All preoperative neurological examinations were nondiagnostic.

Radiological Data. Pretherapeutic MR imaging revealed, according to the classification of Yaşargil et al.,⁸⁴ the following locations: 5 patients, Type 3B; 6 patients, Type 5A; and 13 patients, Type 5B.

Neuropathological Data. The neuropathological examination led to the diagnosis of 21 WHO Grade II oligodendrogliomas, 2 WHO Grade II oligoastrocytomas, and 1 WHO Grade II astrocytoma.

Oncological Strategies. From an oncological point of view, various strategies were considered. Among the first-line strategies were 12 WS cases, 1 case of TMZ- and 1 PCV-based chemotherapeutic treatments, and 10 surgery cases. Among the second-line strategies were 1 WS

TABLE 4: Seizure evolution in patients who underwent surgery*

Case No.	1st Tx	Seizure Grade After 1st Tx	2nd Tx	Seizure Grade After 2nd Tx	3rd Tx	Seizure Grade After 3rd Tx	4th Tx	Seizure Grade After 4th Tx	FU
S1	PCV × 2	EI	TMZ × 24	EI	WS→AT	—	surgery	—	RT, F, PC, & death
S2	surgery	EII	—	—	—	—	—	—	—
S3	surgery	EI	WS	EI	—	—	—	—	—
S4	WS	EIV	surgery	EI (1 yr) then EIV	TMZ × 17→AT	EII then EIV	RT	EII	BI, PC, & death
S5	surgery	EI (9 mos) then EIV	TMZ × 24	EII	WS→AT	EIV	RT	—	current: RT
S6	TMZ × 1	EIV	RT	EII (4 yrs) then EIV	TMZ × 12→AT	EIV	surgery	EI	current: BI (after surgery)
S7	surgery	EI (2 years) then EII	—	—	—	—	—	—	current: WS
S8	WS	EIV	TMZ × 12	EI	surgery	EII	—	—	current: WS
S9	WS	EIV	surgery	EIII	WS	EIV→AT	RT	EII (4 mos) then EIV	current: TMZ × 9
S10	WS	EI	surgery	EI	—	—	—	—	current: WS
S11	S1	EI (7 mos) then EIII	TMZ × 12	EII	S2	EII	—	—	current: WS
S12	surgery	EIII then EIV	TMZ	EIV then EIII then EII then EIV	RT	EIV then EIII	—	—	current: WS
S13	WS	EII	surgery	EI	TMZ × 8→AT	EI	RT	EI	PCV, PC, & death
S14	WS	EII	surgery	EI	—	—	—	—	current: WS
S15	WS	EI	surgery	EI, †AE	—	—	—	—	current: WS
S16	surgery	EII	—	—	—	—	—	—	current: WS
S17	biopsy + surgery	EI (3 yrs)	TMZ × 12	EI (10 mos) then EII→AT	RT	EII	PC	EIII	—
S18	WS	EIII	TMZ × 14	EII	surgery	EI (1 yr) then EII (2 yrs) then EIII	—	—	new Tx envisioned
S19	S1	EI	S2	EI then EII	TMZ × 3	EI	—	—	current: TMZ
S20	WS	EIV	surgery	EIV	TMZ × 22→AT	EIII	RT	EII	CE, PC, & death
S21	WS	EIV	BBSFOP	EI	WS	EIV	surgery	EIII and then EIV	current: TMZ
S22	WS	EII	PCV × 6	EII	RT	EI	surgery	EI (6 yrs) then EII	current: WS
S23	WS	EIV	surgery	EI	TMZ × 12	EI	PCV × 4→AT	EI	RT, CE, PC, & death
S24	S1	EI (2 yrs) then EII	S2 (2nd localization)	EI (6 mos) then EII	TMZ × 3	EI	RT	—	PCV, CE, & death (sepsis)

* BBSFOP = cisplatin + etoposide + vincristine + cyclophosphamide.

case, 7 TMZ cases, 1 PCV case, 1 radiotherapy case, and 10 surgery cases; among the third-line strategies were 7 TMZ cases, 2 radiotherapy cases, and 3 surgery cases; and among the fourth-line strategies were 1 PCV case, 6 radiotherapy cases, and 4 surgery cases.

Epilepsy. Seizure(s) was the first symptom in all surgical cases except 1. During the initial period, according to our database classification, seizure frequency was con-

sidered to be occasionally (11 cases), monthly (9 cases), weekly (2 cases), and daily (1 case). During the course of their epileptic disease, 10 patients were treated with a 1 AED, 5 with 2 AEDs, 4 with 3 AEDs, and 4 with 4 AEDs. On the whole, 11 patients were treated with monotherapy and 10 with polytherapy.

The course of epilepsy varied according to the different first-line strategies. After close monitoring as the

TABLE 5: Summary of data on chemotherapy*

Group	Case No.	Seizure Baseline	Pre-CT Engel Grade	Post-CT Engel Grade
nonsurgical				
first-line CT				
TMZ	1	—	—	—
	6	O	EIII	EI
	7	M	EIV	EII
	10	M	EIII	EI
second-line CT				
TMZ	2	O	EIII	EI
	4	M	EIV	EII
	8	O	EI	EI
	9	W	EI	EI
	14	M	EIV	EIII
	17	O	EII	EI
	19	D	EIV	EI
	21	D	EIV	EIII
	22	M	EIV	EII
PCV	1	—	—	—
	15	M	EIII	EIII
	18	M	EIV	EI
	20	D	EIV	EII
fotemustine	16	O	EIII	EIV
surgical				
first-line CT				
TMZ	S6	M	EIV	EIV
PCV	S1	—	—	—
second-line CT				
TMZ	S1	—	—	—
	S5	W	EIV	EII
	S8	O	EIV	EI
	S11	M	EIII	EII
	S12	D	EIII	EII

* CT = chemotherapy.

first-line strategy, the condition of ~ 40% of the patients improved considerably with AED treatment only (EI: 2 patients, EII: 3 patients) and modestly improved, stabilized, or deteriorated in 60% (EIII: 1 patients, EIV: 6 patients) despite the AED treatment. After surgery as a first-line treatment, 90% of patients had improvement (EI: 7 patients, EII: 2 patients) and 10% stabilized. After first-line TMZ-based chemotherapy, all the patients improved.

After second-line surgical treatment, ~ 80% of patients improved (EI: 9 patients, EII: 0) and ~ 20% stabilized or deteriorated (EIII: 1 patient, EIV: 1 patient). After chemotherapy-based treatment (1 PCV and 7 TMZ), 8 of 8 patients had improvement (EI: 4 patients, EII: 4 patients).

The number of patients is too limited to report the results of radiotherapy and third- or fourth-line treatments.

Discussion

Our results confirm that seizures represent a key issue in GIGs and that surgery and chemotherapy can be effective treatments.

Seizures and Insular Gliomas

The mechanism of epilepsy in patients with brain tumors is clearly multifactorial.¹³ Its incidence depends mainly on tumor type and location. The relation between a WHO Grade II glioma and an insular topography constitutes an association of negative factors. Indeed, patients with slowly progressive brain tumors (typically WHO Grade II gliomas) are known to frequently present with seizures in > 80% of cases, and intractable epilepsy is induced in at least 15% of cases.^{3,6,7,11,16–18,21,32,33,48,53,54,57,63,79,85}

The participation of the insular cortex in epilepsy remains poorly understood because there are a limited number of works on the topic given the conceptual and surgical^{22,23,27,37,45,60,66,69} difficulties in studying this complex structure in the interface between the limbic system and the neocortex. The number of dedicated studies is very limited.^{16,20,22,23,27,30,43,45,58,59,66,69,84,86} Nevertheless, much data recently obtained via technical progress in the electrophysiological exploration of insular cortex^{43,66} appear to implicate this area in pharmacologically resistant seizures.^{1,52} Consequently, the frequency of seizures originating from the insular cortex is probably underestimated and often incorrectly attributed to mesiotemporal structures.^{2,14,17,20,30,35,43,58,59,82,83,86}

In our series, epilepsy remains a major problem with 4 (9%) of 41 patients with daily, 5 (11%) of 41 with weekly, and 18 (42%) of 41 with monthly seizures. Thus, the impact on quality of life seems very major.^{18,73}

Antiepileptic Drugs and Seizures

The hepatic cytochrome P450 (CYP) isoenzyme system and glucuronyl transferase (GT) enzymes metabolize many drugs. The coadministration of enzyme-inducing AEDs with various treatments can lead to clinically relevant interactions by the induction or inhibition of enzymes. These interactions can cause insufficient tumor and seizure control or lead to unforeseen toxicity.

Enzyme-inducing AEDs, such as carbamazepine, oxcarbazepine, phenytoin, topiramate (high dose), and phenobarbital, can drastically reduce the serum concentration of associated drugs, which are substrates of the same enzymes, and notable levels and effects of antineoplastics^{77,78} by compromising antitumor activity. Moreover, patients taking enzyme-inducing AEDs for > 2 years (often the case for those with WHO GIGs) and those > 40 years of age (not exceptional in this population) have significantly lower bone mineral density at clinically relevant fracture risk sites.⁶² In contrast, valproic acid is an enzyme inhibitor and may therefore lead to toxic levels of simultaneously administered chemotherapeutic agents, such as etoposide, platinum salts, or nitrosoureas,⁵⁶ and might be responsible for an increasing hematotoxicity.⁹

For all of these reasons, enzyme-inducing AED use and, to a lesser degree, enzyme-inhibiting AEDs should be avoided in patients with WHO GIGs—even more when

chemotherapy is planned. It is therefore important to prefer AEDs not metabolized by the P450 system and with a good safety-profile,^{26,50,77} such as levetiracetam,⁵⁰ gabapentin,⁷⁸ pregabalin,⁵⁵ lamotrigine,^{29,38} or lacosamide.¹⁹

It is licit to recommend 1) 1 or 2 successive non-enzyme-inducing AED monotherapies until the maximal doses recommended, unless there are signs of intolerance; and 2) before proceeding to a bitherapy, to avoid the more toxic coprescription of AEDs sharing the same primary mechanism of action.^{36,61} We followed such recommendations with a majority of the non-enzyme-inducing AED mono- or bitherapies and the exceptional tritherapy in the present series. However, more properly designed clinical studies are warranted to raise the level of evidence for robust clinical recommendations.⁷⁵

Surgery and Seizures

Tumors represent the primary pathology in 10–30% of patients undergoing surgical treatment for chronic epilepsy.⁵ Seizures are more frequent in patients with WHO GIIgs and secondary malignant gliomas than other primary tumors of the brain.⁶⁷ The frequency of seizures seems to evolve in parallel with tumor growth.⁸¹ It was verified in the present retrospective series that in a majority of cases, an increase in seizure frequency is correlated with significant tumor growth in cases not transformed (still Grade II).

Insular WHO GIIgs seem to represent a specific etiology of intractable epilepsy in > 50% of cases²⁴ compared with other locations of the same pathology in which drug-resistant seizures were seen in ~ 15% of cases.^{3,6,7,11,13,16,18,21,32,33,41,48,53,54,57,63,79,85} Patients with drug-resistant epilepsy and temporal lobe tumors should undergo evaluation in dedicated oncology and epilepsy surgery programs.⁴⁶

Few published studies have considered surgery in the control of seizures due to insular tumors. This control seems to be reported in ~ 80 to 90% of cases of surgical tumorectomy associated with perilesional cortical resection with or without the removal of mesiotemporal structures,^{66,70,84,86} while preserving or even improving—as with tumors in locations other than the insula—quality of life and survival.^{7,41,70} Even subtotal resection can result in good seizure control.⁸⁰ In the present series after surgery as a first-line strategy, ~ 90% of patients had improvement and 10% stabilized. Furthermore, after surgery as a second-line strategy, ~ 80% of patients had improvement and 10% stabilized. These results perfectly correspond with findings that were first published.²⁴

Note that in our series, the indications for resection were gradually modified. Ten years ago, chemotherapy or radiotherapy was begun after a simple biopsy procedure. As surgical techniques have advanced, especially intraoperative functional mapping with cortical and subcortical stimulations, indications for surgery have become more numerous. At present, a first-intention resection to functional and anatomical limits (within the anterior perforating substance and the posterior part of the dominant insula) is discussed. Indications are based more on oncological than epileptological reasons. Intraoperative electrocorticography is not used. Resection is pushed until the functional boundaries, which are identified using

corticosubcortical electrostimulation. As a consequence, even if a seizure focus was detected by electrocorticography beyond these limits, it would not have been possible to remove it for functional reasons.²³ In addition, no specific part of the insula was recognized as being more specifically involved in the epileptogenesis. The effect on seizures seems to be due more to the extent of surgery.¹³ During the postsurgical period, antiepileptic treatment is pursued. In cases of complete surgery and an absence of seizures, we recommend a progressive decrease in and then arrest of treatment 1 year after surgery. For the opposite situation (incomplete surgery)—except in patients with a long seizure-free period—we usually recommend pursuit of the treatment and most often a monotherapy at the lowest level.

Chemotherapy and Seizures

For growing nonsurgical tumors (or following an incomplete resection), when AEDs no longer control seizures or when other symptoms become more marked (cognitive impairment, focal signs), direct tumor treatment as opposed to symptom treatment should be considered. Among these, chemotherapy has taken a more and more important role in the last few years and should be systematically discussed. Many theoretical arguments, such as subnormal blood-brain or blood-tumor barrier or low proliferation indices, must be considered against chemotherapy's potential efficiency for this type of tumor. Note that the first and only published randomized Phase III trial of chemotherapy for low-grade gliomas was conducted by the Southwestern Oncology Group. Radiotherapy alone was compared with radiotherapy plus lomustine chemotherapy after subtotal/partial surgery or biopsy. No benefit was demonstrated, and the trial was prematurely terminated.

Nevertheless, we have more and more data allowing us to propose this treatment in symptomatic patients. MacDonald et al.⁴⁹ have been the first, in a study of aggressive oligodendrogliomas, to suggest the possibility of an objective response in low-grade tumors. Six years later, Mason et al.⁵¹ noted 9 of 9 responders (8 patients at presentation and 1 patient at a recurrence after radiotherapy) treated with a PCV regimen while Soffietti et al.⁷¹ reported on 13 of 13 stabilized or responsive patients treated with PCV. More recently, Buckner et al.¹⁵ have described a series of 29 patients treated with PCV and noted an objective response in 28%, but chemotherapy was immediately followed by radiotherapy in this series. Brada et al.¹⁰ have treated 10 patients with TMZ for newly diagnosed oligodendrogliomas and observed 2 partial responses and 3 minor responses. The multicentric study described by Quinn et al.⁶⁵ was based on TMZ chemotherapy in 46 patients with tumor progression, a majority with astrocytomas and 14 patients pretreated with radiotherapy and chemotherapy. Sixty-one percent of objective responses were noted. Progression-free survival for the entire group was 22 months. Seventy-six percent were in a period of progression-free survival at 12 months from the beginning of treatment. Hoang-Xuan et al.⁴² have reported their experience treating 60 patients according to a conventional TMZ schedule (200 mg/m²/day for 5 days

every 28 days). The median number of delivered chemotherapy cycles was 11. More than one-half of the patients had clinical improvement. A radiologically demonstrated objective response was noted in one-third of the cases. Only 8% of the patients were considered to be in tumor progression during the treatment period. The only factor correlated with the treatment response was the loss of chromosome 1p. Results followed suit for Stege et al.⁷² who delivered PCV chemotherapy treatment for low-grade gliomas. He treated 16 patients with a new diagnosis and 5 patients at recurrence and observed 13 and 3 respective responses with a median time to disease progression up to 24 months. Frenay et al.³¹ have also reported their PCV experience in 10 patients with pure WHO Grade II astrocytomas, with clear clinical improvement in all cases. Sixty percent of the patients became seizure free at the end of the treatment despite the fact that pharmacologically resistant epilepsy had developed in all patients before chemotherapy. Finally, Lebrun et al.⁴⁷ have reported the outcome in 33 consecutive patients with a pure WHO GIIIG. Ninety percent of these patients remained progression free at 1 year after treatment with very good long-term results from an epileptic point of view. In the present study, 26 patients were treated with chemotherapy as a first- or second-line treatment for progressive tumors: TMZ was used in 19 cases, PCV in 6 cases, and fotemustine in 1 case. A major improvement in the frequency of seizures (gain of 2 Engel classes) was observed in 11 cases while the AEDs were not modified. A clear improvement (gain of 1 Engel class) was observed in 5 cases. An absence of modification or an escalation in seizure frequency was noticed in 3 cases. Six patients did not present with any seizure before or after chemotherapy. Notably, chemotherapy led to excellent results from an epileptic point of view in 16 (84.2%) of 19 cases.

We have just seen that the historic association of PCV or more recent monotherapy with TMZ can provide clear symptomatic improvements in epilepsy due to insular GIIIG despite the fact that few authors have specifically considered this point at all^{10,42} and even more rarely in detail.^{31,47} Data in the literature remain especially exceptional for an insular location. Note that the tolerance of this treatment is not perfect. The PCV association has a cumulative hematological toxicity, rendering the administration of > 4 or 6 courses difficult without serious adverse events. The peripheral neurological risk of the vincristine or the risk of lung fibrosis with the lomustine should not to be neglected. Patients frequently report an intense asthenia or a loss of weight. Gonadic toxicity also seems frequent.

The prescription of TMZ with various modalities¹² would eventually be more adapted to this type of tumor without the cumulative hematological toxicity despite very prolonged treatments (24 months and sometimes more). It will be necessary to consider the risk of lymphocytopenia, especially with continuous treatment plans, and in some cases a preventive treatment of opportunistic infections, notably pneumocystosis.³⁴ The risk of cutaneous eruption and even of liver toxicity should not be underscored, and no data are available concerning potential gonadic toxicity.

Finally, it is reasonable to think that chemotherapy is able to improve the quality of life.^{8,10,15,42,47,72} In practice,

our present tendency is to favor this type of treatment as a first-line strategy for nonoperable tumors or on the relapse of gliomas incompletely removed, in case of clinical (epileptological) and/or significant radiological progression. Our aims are as follows: 1) clear clinical efficiency translated into a relief of seizures, a decrease in AEDs (number and dosage), better social implications, and thus an improvement in quality of life; 2) the opportunity to envisage subtotal or total resection when complete removal was not possible during the first resection, thanks to shrinkage induced by the chemotherapy²⁵ (6 patients in this series [Cases S1, S6, S8, S18, S21, and S22] have had such a benefit from surgery after 1 or 2 lines of chemotherapy); and 3) the ability to delay radiotherapy because of its potential neurocognitive side effects, especially when delivered to large volumes and functional areas.^{73,74}

It is nevertheless imperative to confirm these hypotheses, to set up clinical trials, and to associate with them a number of ancillary works connected to biological, pathological, radiological, epileptological, functional, neurocognitive, and economic questions.

We would have liked to write an identical paragraph concerning radiotherapy and, more precisely, the impact of radiotherapy on seizures due to an insular GIIIG. Regrettably, the data in the literature⁶⁸ and the cases in the present series (in which radiotherapy was kept for progression after surgery and/or chemotherapy) are rare. Nevertheless, they have allowed us, contrary to authors of the majority of published articles, to obtain a “pure” and unique vision concerning the impact of a specific treatment (chemotherapy) on a specific symptom (seizure) at a precise location (insula).

Conclusions

The analysis of the literature and this unique series allowed us to consolidate the concept that surgery, despite any technical difficulties, could be indicated in pharmacoresistant epilepsy due to insular glioma independently of the oncological indications. We also demonstrated that chemotherapy (TMZ or PCV) could also be an effective weapon against seizures. It is obvious that a combined version of these 2 therapeutic modalities must be used in daily practice. It requires close collaboration between neurosurgeons and neurooncologists and an adaptation of strategies to each individual case for optimal preservation, as long as possible, of the quality of life. Finally, progress—not just in terms of improved surgical techniques and new drug development—should be based on a better systematic longitudinal collection and an analysis of both neurocognition parameters and quality of life with new adapted scales.

Disclaimer

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References

1. Augustine JR: Circuitry and functional aspects of the insular lobe in primates including humans. **Brain Res Brain Res Rev** 22:229–244, 1996
2. Aziz Q, Anderson JC, Valind S, Sundin A, Hamdy S, Jones

- AK, et al: Identification of human brain loci processing oesophageal sensation using positron emission tomography. **Gastroenterology** 113:50–59, 1997
3. Bartolomei JC, Christopher S, Vives K, Spencer DD, Piepmeier JM: Low-grade gliomas of chronic epilepsy: a distinct clinical and pathological entity. **J Neurooncol** 34:79–84, 1997
4. Bauchet L, Rigau V, Mathieu-Daudé H, Figarella-Branger D, Hugues D, Palusseau L, et al: A French brain tumor data bank: methodology and first results on 10,000 cases. **J Neurooncol** 84:189–199, 2007
5. Bauer R, Dobesberger J, Unterhofer C, Unterberger I, Walser G, Bauer G, et al: Outcome of adult patients with temporal lobe tumours and medically refractory focal epilepsy. **Acta Neurochir (Wien)** 149:1211–1216, 2007
6. Berger MS: Functional mapping-guided resection of low-grade gliomas. **Clin Neurosurg** 42:437–452, 1995
7. Berger MS, Ghatan S, Haglund MM, Dobbins J, Ojemann GA: Low-grade gliomas associated with intractable epilepsy: seizure outcome utilizing electrocorticography during tumor resection. **J Neurosurg** 79:62–69, 1993
8. Byrne TN: Response of low-grade oligodendroglial tumors to temozolomide. **J Neurooncol** 70:279–280, 2004
9. Bourg V, Lebrun C, Chichmanian RM, Thomas P, Frenay M: Nitroso-urea-cisplatin-based chemotherapy associated with valproate: increase of hematologic toxicity. **Ann Oncol** 12:217–219, 2001
10. Brada M, Viviers L, Abson C, Hines F, Britton J, Ashley S, et al: Phase II study of primary temozolomide chemotherapy in patients with WHO II grade gliomas. **Ann Oncol** 14:1715–1721, 2003
11. Britton JW, Cascino GD, Sharbrough FW, Kelly PJ: Low-grade neoplasms and intractable partial epilepsy: efficacy of surgical treatment. **Epilepsia** 35:1130–1135, 1994
12. Brock CS, Newlands ES, Wedge SR, Bower M, Evans H, Colquhoun I, et al: Phase I trial of temozolomide using an extended continuous oral schedule. **Cancer Res** 58:4363–4367, 1998
13. Brogna C, Gil Robles S, Duffau H: Brain tumors and epilepsy. **Expert Rev Neurother** 8:941–955, 2008
14. Buchel C, Morris J, Dolan RJ, Friston KJ: Brain systems mediating aversive conditioning: an event related fMRI study. **Neuron** 20:947–957, 1998
15. Buckner JC, Gesme D Jr, O'Fallon JR, Hammack JE, Stafford S, Brown PD, et al: Phase II trial of procarbazine, lomustine and vincristine as initial therapy for patients with low-grade oligodendroglioma or oligoastrocytoma: efficacy and associations with chromosomal abnormalities. **J Clin Oncol** 21:251–255, 2003
16. Cascino GD: Epilepsy and brain tumors: implication for treatment. **Epilepsia** 31:37–44, 1990
17. Cascino GD, Karnes WE: Gustatory and second sensory seizures associated with lesions in the insular cortex seen on magnetic resonance imaging. **J Epilepsy** 3:185–187, 1990
18. Chang EF, Potts MB, Keles GE, Lamborn Kr, Chang SM, Barbaro NM, et al: Seizure characteristics and control following resection in 332 patients with low-grade gliomas. **J Neurosurg** 108:227–235, 2008
19. Cross SA, Curran MP: Lacosamide: in partial-onset seizures. **Drugs** 69:449–459, 2009
20. Cukiert A, Forster C, Andrioli MS, Frayman L: Insular epilepsy. Similarities to temporal lobe epilepsy. Case report. **Arq Neuropsiquiatr** 56:126–128, 1998
21. Devaux B, Chassoux F, Landre E, Turak B, Daumas-Duport C, Chagot D, et al: Chronic intractable epilepsy associated with a tumor located in the central region: functional mapping data and postoperative outcome. **Stereotact Funct Neurosurg** 69:229–238, 1997
22. Duffau H, Bauchet L, Lehericy S, Capelle L: Functional compensation of the left dominant insula for language. **Neuroreport** 12:2159–2163, 2001
23. Duffau H, Capelle L, Lopes M, Faillot T, Sichez JP, Fohanno D: The insular lobe: physiopathological and surgical considerations. **Neurosurgery** 47:801–811, 2000
24. Duffau H, Capelle L, Lopes M, Bitar A, Sichez JP, van Effenterre R: Medically intractable epilepsy from insular low-grade gliomas: improvement after an extended lesionectomy. **Acta Neurochir (Wien)** 144:563–573, 2002
25. Duffau H, Taillandier L, Capelle L: Radical surgery after chemotherapy: a new therapeutic strategy to envision in grade II glioma. **J Neurooncol** 80:171–176, 2006
26. Dupont S: [Epilepsy and brain tumors.] **Rev Neurol (Paris)** 164:517–522, 2008 (Fr)
27. Ebeling U, Kothbauer K: Circumscribed low grade astrocytomas in the dominant opercular and insular region: a pilot study. **Acta Neurochir (Wien)** 132:66–74, 1995
28. Engel J Jr: Alternative therapy, in Engel J Jr (ed): **Seizures and epilepsy**. Philadelphia, PA: FA Davis, 1990, pp 443–474
29. Fadul CE, Meyer LP, Jobst BC, Cornell CJ, Lewis LD: Agranulocytosis associated with lamotrigine in a patient with low-grade glioma. **Epilepsia** 43:199–200, 2002
30. Fiol ME, Leppik IE, Mireles R, Maxwell R: Ictus emeticus and the insular cortex. **Epilepsy Res** 2:127–131, 1988
31. Frenay MP, Fontaine D, Vandebos F, Lebrun C: First-line nitrosourea-based chemotherapy in symptomatic non-resectable supratentorial pure low-grade astrocytomas. **Eur J Neurol** 12:685–690, 2005
32. Fried I: Management of low-grade gliomas: results of resections without electrocorticography. **Clin Neurosurg** 42:453–463, 1995
33. Fried I, Kim JH, Spencer DD: Limbic and neocortical gliomas associated with intractable seizures: a distinct clinicopathological group. **Neurosurgery** 34:815–824, 1994
34. Gajewski TF: Temozolomide for melanoma: new toxicities and new opportunities. **J Clin Oncol** 22:580–581, 2004
35. Ghaem O, Mellet E, Crivello F, Tzourio N, Mazoyer B, Berthoz A, et al: Mental navigation along memorized routes activates the hippocampus precuneus and insula. **Neuroreport** 8:739–744, 1997
36. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Chadwick D, Guerreiro C, et al: ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. **Epilepsia** 47:1094–1120, 2006
37. Haglund MM, Berger MS, Kunkel DD, Franck JE, Ghatan S, Ojemann GA: Changes in gamma-aminobutyric acid and somatostatin in epileptic cortex associated with low-grade gliomas. **J Neurosurg** 77:209–216, 1992
38. Hennessy MJ, Wiles CM: Lamotrigine encephalopathy. **Lancet** 347:974–975, 1996
39. Hildebrand J: Management of epileptic seizures. **Curr Opin Oncol** 16:314–317, 2004
40. Hildebrand J, Lecaillon C, Perennes J, Delattre JY: Epileptic seizures during follow up of patients treated for primary brain tumors. **Neurology** 65:212–215, 2005
41. Hiremath GK, Bingaman WE, Prayson RA, Nair D: Oligoastrocytoma presenting with intractable epilepsy. **Epileptic Disord** 9:315–322, 2007
42. Hoang-Xuan K, Capelle L, Kujas M, Taillibert S, Duffau H, Lejeune J, et al: Temozolomide as initial treatment for adults with low grade oligodendrogliomas or oligoastrocytomas and correlation with chromosome 1p deletions. **J Clin Oncol** 22:3133–3138, 2004
43. Isnard J, Guenot M, Ostrowsky K, Sindou M, Mauguier F: The role of the insular cortex in temporal lobe epilepsy. **Ann Neurol** 48:614–623, 2000
44. Kirkpatrick PJ, Honavar M, Janota I, Poltrey CE: Control of temporal lobe epilepsy following en bloc resection of low-grade tumors. **J Neurosurg** 78:19–25, 1993
45. Lang FF, Olansen NE, DeMonte F, Gokaslan ZL, Holland EC, Kalhorn C, et al: Surgical resection of intrinsic insular tumors: complication avoidance. **J Neurosurg** 95:638–650, 2001
46. Laws ER Jr, Taylor WF, Clifton MB, Okazaki H: Neurosur-

- gical management of low-grade astrocytomas of the cerebral hemispheres. **J Neurosurg** **61**:665–673, 1984
47. Lebrun C, Fontaine D, Bourg V, Ramaoli A, Chanalet S, Vandebos F, et al: Treatment of newly diagnosed symptomatic pure low-grade oligodendrogliomas with PCV chemotherapy. **Eur J Neurol** **14**:391–398, 2007
 48. Lombardi D, Marsh R, De Tribolet N: Low grade glioma in intractable epilepsy: lesionectomy versus epilepsy surgery. **Acta Neurochir Suppl** **68**:70–74, 1997
 49. MacDonald DR, Cascino TL, Schold SC Jr, Cairncross JG: Response criteria for phase II studies of supratentorial malignant glioma. **J Clin Oncol** **8**:1277–1280, 1990
 50. Maschio M, Dinapoli L, Zarabia A, Jandolo B: Issues related to the pharmacological management of patients with brain tumours and epilepsy. **Funct Neurol** **21**:15–19, 2006
 51. Mason WP, Krol GS, DeAngelis LM: Low grade oligodendroglioma responds to chemotherapy. **Neurology** **46**:203–207, 1996
 52. Mesulam MM, Mufson E: The insula of Reil in man and monkey, in Jones GE, Peters AA (eds): **Cerebral Cortex**. New York: Plenum Press, pp 179–225, 1985
 53. Morris HH, Estes ML, Gilmore R, Van Ness PC, Barnett GH, Turnbull J: Chronic intractable epilepsy as the only symptom of primary brain tumor. **Epilepsia** **34**:1038–1043, 1993
 54. Morris HH, Matkovic Z, Estes ML, Prayson RA, Comair YG, Turnbull J, et al: Ganglioglioma and intractable epilepsy: clinical and neurophysiologic features and predictors of outcome after surgery. **Epilepsia** **39**:307–313, 1998
 55. Novy J, Stupp R, Rossetti AO: Pregabalin in patients with primary brain tumors and seizures: a preliminary observation. **Clin Neurol Neurosurg** **111**:171–173, 2009
 56. Oberndorfer S, Piribauer M, Marosi C, Lahrmann H, Hitznberger P, Grisold W: P450 enzyme inducing and non-enzyme inducing antiepileptics in glioblastoma patients treated with standard chemotherapy. **J Neurooncol** **72**:255–260, 2005
 57. Olivier A, Lacerte D: Epilepsy and benign gliomas, in Apuzzo MLJ (ed): **Low Grade Glioma**. New York: AANS, 1995, pp 347–379
 58. Ostrowsky K, Isnard J, Ryvlin P, Guénot M, Fisher C, Mauguier F: Functional mapping of the insular cortex: clinical implication in temporal lobe epilepsy. **Epilepsia** **41**:681–686, 2000
 59. Penfield W, Faulk ME Jr: The insula: further observations on its function. **Brain** **78**:445–470, 1955
 60. Penfield W, Jasper H: **Epilepsy and the Functional Anatomy of the Human Brain**. Boston: Little Brown, 1954
 61. Perucca E, Hedges A, Makki KA, Ruprah M, Wilson JF, Richens A: A comparative study of the relative enzyme inducing properties of anticonvulsant drugs in epileptic patients. 1984. **Br J Clin Pharmacol** **58**:S854–S863, 2004
 62. Petty SJ, Paton LM, O'Brien TJ, Makovey J, Erbas B, Sambrook P, et al: Effect of antiepileptic medication on bone mineral measures. **Neurology** **65**:1358–1365, 2005
 63. Piepmeier JM: Observations on the current treatment of low-grade astrocytic tumors of the cerebral hemispheres. **J Neurosurg** **67**:177–181, 1987
 64. Pilcher WH, Silbergeld DL, Berger MS, Ojemann GA: Intraoperative electrocorticography during tumor resection: impact on seizure outcome in patients with gangliogliomas. **J Neurosurg** **78**:891–902, 1993
 65. Quinn JA, Reardon DA, Friedman AH, Rich JN, Sampson JH, Provenzale JM, et al: Phase II trial of temozolomide in patients with progressive low-grade glioma. **J Clin Oncol** **21**:646–651, 2003
 66. Roper SN, Lévesque MF, Sutherland WW, Engel J Jr: Surgical treatment of partial epilepsy arising from the insular cortex. **J Neurosurg** **79**:266–269, 1993
 67. Rosati A, Tomassini A, Pollo B, Ambrosi C, Schwarz A, Padovani A, et al: Epilepsy in cerebral glioma: timing of appearance and histological correlations. **J Neurooncol** **93**:395–400, 2009
 68. Shankar A, Rasjshekhar V, Shankar A, Rajshekhar V: Radiological and clinical outcome following stereotactic biopsy and radiotherapy for low grade insular astrocytoma. **Neurol India** **51**:503–506, 2003
 69. Silfvenius H, Gloor P, Rasmussen T: Evaluation of insular ablation in surgical treatment of temporal lobe epilepsy. **Epilepsia** **5**:307–320, 1964
 70. Simon M, Neuloh G, von Lehe M, Meyer B, Schramm J: Insular gliomas: the case for surgical management. **J Neurosurg** **110**:685–695, 2009
 71. Soffietti R, Ruda R, Bradac GB, Schiffer D: PCV chemotherapy for recurrent oligodendrogliomas and oligoastrocytomas. **Neurosurgery** **43**:1066–1073, 1998
 72. Stege EM, Kros JM, De Bruin HG, Enting RH, Van Heuvel I, Looijenga LH, et al: Successful treatment of low grade oligodendroglioma tumors with a chemotherapy regimen of procarbazine, lomustine and vincristine. **Cancer** **103**:802–809, 2005
 73. Taphoorn MJ: Neurocognitive sequelae in the treatment of low-grade gliomas. **Semin Oncol** **30** (19 Suppl):45–48, 2003
 74. Taphoorn MJ, Klein M: Cognitive deficits in adult patients with brain tumours. **Lancet Neurol** **3**:159–168, 2004
 75. Tibussek D, Distelmaier F, Schönberger S, Göbel U, Mayatepek E: Antiepileptic treatment in paediatric oncology—an interdisciplinary challenge. **Klin Padiatr** **218**:340–349, 2006
 76. Vanaclocha V, Saiz-Sapena N, Garcia-Casasola C: Surgical treatment of insular gliomas. **Acta Neurochir (Wien)** **139**:1126–1135, 1997
 77. Vecht CJ, Wagner GL, Wilms EB: Interactions between anti-epileptic and chemotherapeutic drugs. **Lancet Neurol** **2**:404–409, 2003
 78. Vecht CJ, Wagner GL, Wilms EB: Treating seizures in patients with brain tumors: Drug interactions between anti-epileptic and chemotherapeutic agents. **Semin Oncol** **30** (6 Suppl 19):49–52, 2003
 79. Villemure JG, De Tribolet N: Epilepsia in patients with central nervous system tumors. **Curr Opin Neurol** **9**:424–428, 1996
 80. von Lehe M, Lutz M, Kral T, Schramm J, Elger CE, Clusmann H: Correlation of health-related quality of life after surgery for mesial temporal lobe epilepsy with two seizure outcome scales. **Epilepsy Behav** **9**:73–82, 2006
 81. Wick W, Menn O, Meisner C, Steinbach J, Hermisson M, Tatagiba M, et al: Pharmacotherapy of epileptic seizures in glioma patients: who, when, why and how long? **Onkologie** **28**:391–406, 2005
 82. Wieser HG: **Electroclinical Features of the Psychomotorseizure**. Stuttgart: Gustav Fisher, 1983
 83. Xu X, Fukuyama H, Yazawa S, Mima T, Hanakawa T, Magata Y, et al: Functional localization of pain perception in the human brain studied by PET. **Neuroreport** **8**:555–559, 1997
 84. Yaşargil MG, von Ammon K, Cavazos E, Doczi T, Reeves JD, Roth P: Tumours of the limbic and paralimbic systems. **Acta Neurochir (Wien)** **118**:40–52, 1992
 85. Zentner J, Hufnagel A, Wolf HK, Ostertun B, Behrens E, Campos MG, et al: Surgical treatment of neoplasms associated with medically intractable epilepsy. **Neurosurgery** **41**:378–387, 1997
 86. Zentner J, Meyer B, Stangl A, Schramm J: Intrinsic tumors of the insula: a prospective study of 30 patients. **J Neurosurg** **85**:263–271, 1996

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