Neurosurg Rev
DOI 10.1007/s10143-016-0771-2

ORIGINAL ARTICLE

Brain tumors in eloquent areas: A European multicenter survey of intraoperative mapping techniques, intraoperative seizures occurrence, and antiepileptic drug prophylaxis

Giannantonio Spena[1] · Philippe Schucht[2] · Kathleen Seidel[3] · Geert-Jan Rutten[4] · Christian Franz Freyschlag[5] · Federico D'Agata[6] · Emanule Costi[1] · Francesca Zappa[1] · Marco Fontanella[1] · Denys Fontaine[7] · Fabien Almairac[7] · Michele Cavallo[8] · Pasquale De Bonis[8] · Gerardo Conesa[9] · Nicholas Foroglou[10] · Santiago Gil-Robles[11] · Emanuel Mandonnet[12] · Juan Martino[13] · Thomas Picht[14] · Catarina Viegas[15] · Michel Wager[16] · Johan Pallud[17]

Received: 9 March 2016 / Revised: 5 July 2016 / Accepted: 25 July 2016

Abstract Intraoperative mapping and monitoring techniques for eloquent area tumors are routinely used world wide. Very few data are available regarding mapping and monitoring methods and preferences, intraoperative seizures occurrence and perioperative antiepileptic drug management. A questionnaire was sent to 20 European

Electronic supplementary material The online version of this article (doi:10.1007/s10143-016-0771-2) contains supplementary material, which is available to authorized users.

✉ Giannantonio Spena
giannantonios@hotmail.com; giannantonios@gmail.com

Philippe Schucht
philippe.schucht@insel.ch

Kathleen Seidel
kathleen.seidel@insel.ch

Geert-Jan Rutten
geertjanrutten@hotmail.com

Christian Franz Freyschlag
christian.freyschlag@uki.at

Federico D'Agata
federico.dagata@unito.it

Fabien Almairac
almairac.f@chu-nice.fr

Michele Cavallo
m.cavallo@ospfe.it

Pasquale De Bonis
p.debonis@ospfe.it

Gerardo Conesa
18419gcb@comb.cat

Nicholas Foroglou
nforoglou@auth.gr

Santiago Gil-Robles
santigilrob@yahoo.es

Emanuel Mandonnet
mandonnet@mac.com

Juan Martino
juan.martino@hotmail.com

Thomas Picht
thomas.picht@charite.de

Catarina Viegas
cata_pv@hotmail.com

Michel Wager
michel.wager@orange.fr

Johan Pallud
johanpallud@hotmail.com

1 Clinic of Neurosurgery, Spedali Civili di Brescia, Scala 7, Piano 3°, Piazzale Spedali Civili 1, 25121 Brescia, Italy

2 Neurosurgery, Bern University Hospital, Bern, Switzerland

3 Neurology, Bern University Hospital, Bern, Switzerland

4 Neurosurgery, St Elisabeth Hospital, Tilburg, the Netherlands

5 Neurosurgery, Medical University of Innsbruck, Innsbruck, Austria

6 Neuroscience, University of Turin, Turin, Italy

Published online: 01 August 2016

centers with experience in intraoperative mapping or neurophysiological monitoring for the treatment of eloquent area tumors. Fifteen centers returned the completed questionnaires. Data was available on 2098 patients. 863 patients (41.1%) were operated on through awake surgery and intraoperative mapping, while 1235 patients (58.8%) received asleep surgery and intraoperative electrophysiological monitoring or mapping. There was great heterogeneity between centers with some totally AW oriented (up to 100%) and other almost totally ASL oriented (up to 92%) (31% SD). For awake surgery, 79.9% centers preferred an asleep-awake-asleep anesthesia protocol. Only 53.3% of the centers used ECoG or transcutaneous EEG. The incidence of intraoperative seizures varied significantly between centers, ranging from 2.5% to 54% ($p < 0.001$). It there appears to be a statistically significant link between the mastery of mapping technique and the risk of intraoperative seizures. Moreover, history of preoperative seizures can significantly increase the risk of intraoperative seizures ($p < 0.001$). Intraoperative seizures occurrence was similar in patients with or without perioperative drugs (12% vs. 12%, $p = 0.2$). This is the first European survey to assess intraoperative functional mapping and monitoring protocols and the management of peri- and intraoperative seizures. This data can help identify specific aspects that need to be investigated in prospective and controlled studies.

Keywords Brain mapping · Brain neoplasms · Epilepsy · Neurophysiological monitoring · Neurosurgeons

[7] Neurosurgery, Centre Hospitalier Universitaire de Nice, Nice, France

[8] Neurosurgery, Sant'Anna di Cona Hospital, Ferrara, Italy

[9] Neurosurgery, Hospital del Mar, Barcelona, Spain

[10] Neurosurgery, AHEPA University Hospital of Thessaloniki, Thessaloniki, Greece

[11] Neurosurgery, Grupo Hospitalario Quirón, Pozuelo de Alarcón, Spain

[12] Neurosurgery, Lariboisiere Hospital, Paris, France

[13] Neurosurgery, Hospital Universitario Marques de Valdecilla, Santander, Spain

[14] Neurosurgery, Charité Universitätsmedizin Berlin, Berlin, Germany

[15] Neurosurgery, Hospital Garcia de Orta, Almada, Portugal

[16] Neurosurgery, Centre Hospitalier Universitaire de Poitiers, Poitiers, France

[17] Neurosurgery, Centre Hospitalier Sainte-Anne and Paris Descartes University, Paris, France

Abbreviations

AAA	awake-awake-awake anesthesia protocol
AED	antiepileptic drug
SAS	asleep-awake-asleep anesthesia protocol
ASL	asleep surgery
AW	awake surgery
ECoG	electrocorticography
EEG	electroencephalography
MEP	motor evoked potential
IS	intraoperative seizure
SD	standard deviation
IQR	interquartile range

Introduction

Resection of brain tumors in eloquent areas requires a balance between a large surgical resection to improve oncological prognosis and functional preservation to maintain an optimal postoperative functional status [1]. The use of intraoperative mapping techniques is fundamental for achieving these two goals [2, 3]. Many neurosurgical centers worldwide routinely perform such functional neurooncological surgery. However, there is large variability in habits and preferences among neurosurgical centers concerning the type of mapping techniques, the choice to awaken a patients, the type of tumor treated, the management of seizures.

Brain mapping techniques can be used both during awake surgery (AW) and asleep surgery (ASL). Penfield et al. [4] introduced direct bipolar stimulation under AW to map both motor and cognitive functions. More recently, in 1993, Taniguchi et al. [5] introduced the short train stimulation technique through motor evoked potentials (MEP) monitoring, and Kombos et al. [6] proposed monopolar stimulation and direct mapping for the resection of motor area tumors under ASL condition [7].

Intraoperative seizures (IS) are a matter of concern, especially in an awake patient, since they can interfere with functional mapping, induce transient or prolonged focal deficit and preclude reliable functional brain mapping, and provoke status epilepticus. Consequently, IS can be cause for premature interruption of tumor resection, as well as postoperative neurological deficits and longer hospital stay [8–10].

The incidence of IS ranges from 0% to 24% (Table 1) and seems to be related to the parameters of the electric stimulation [10]. Several variables may explain this wide range: 1) different definitions for IS; 2) different methodology to detect IS (i.e., evoked potential, EMG activity, EcoG, or direct observation); 3) the anesthetic regimen used (for example, with sevoflurane anesthesia a higher current intensity is required for electrostimulation than with propofol, and therefore the likelihood of IS is higher with the former [8]); 4) the choice of AW or ASL (as the current intensity for electrostimulation

Table 1. The intraoperative seizures (IS) occurrence as reported in the literature over the last 10 years

Author, year	IS occurrence %
Gupta, 2007 [11]	3.8
Kim, 2009 [12]	9
Sacko 2011, [13]	5.7
Deras, 2012 [14]	0
Chacko, 2013 [15]	4.4
Grossman 2013 [16]	2.2
Spena, 2013 [17]	10
Nossek, 2013 [9]	12,6
Beez, 2013 [18]	13,6
Boetto, 2015 [19]	3,4
Hervey-Jumper 2015 [20]	3

is lower in AW than in ASL); 5) the rigor with which the technical principles of electrical stimulation are applied, and the neurosurgeon's experience in the procedure; and 6) the intrinsic epileptogenicity of the tumor. In addition, the association between IS and history of seizures has not been proven. In fact, it is still unclear if patients who had seizures before surgery have a higher risk of developing IS. Furthermore, it has been suggested that young age, low grade of malignancy, and frontal tumor location are associated with an increased risk of IS [9].

All of these aspects need to be clarified to improve the management of IS. Little data is available on the actual situation in centers that routinely use intraoperative mapping techniques with direct electrostimulation. Therefore, we conducted this multicenter survey to envision the protocols and preferences in European centers. On the basis of these evidences, this survey could potentially help focusing on specific aspects that could be investigated in prospective and controlled studies.

Methods

An online questionnaire was sent to 20 European centers with experience in intraoperative mapping or neurophysiological monitoring for the treatment of eloquent area tumors. The questionnaires were sent in May 2014 and the data collection was closed in April 2015. The chart was structured into three parts: A) general information (Sheet 1 in supplemental material); B) epilepsy data (Sheet 2 in supplemental material); and C) data on patients experiencing IS during AW (Sheet 3 in supplemental material). There were 27 questions in all; some were multiple choice questions, while others required brief comments or data. We requested respondents to consider only patients treated in the last 5 years for intracerebral lesions located close to or within eloquent brain areas.

Statistical analysis

Results are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables, and as percentages and frequencies for categorical variables. Univariate analyses were carried out using the chi-square test or Fisher's exact tests for comparing categorical variables, and the unpaired *t* test or Mann–Whitney rank sum test for continuous variables, as appropriate. We used the binomial test to compare an expected frequency with an observed frequency. We used the standardized residual ($z > 2$) for the chi-square post hoc test for comparing multiple categorical variables. For some supplementary analysis, we split the sample into two categories on the basis of relative frequencies of use of AW and ASL(i.e. centers performing AW > ASL and those performing ASL > AW). A p value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed with IBM SPSS Statistics for Windows, Version 20.0.0 (IBM Corp., Armonk, NY, USA).

Results

Awake and asleep surgery

Fifteen centers returned the completed questionnaires. We collected data on 2098 patients; of these, 863 patients (41.1%) had AW and intraoperative mapping and 1235 patients (58.8%) had ASL and intraoperative electrophysiological monitoring or mapping. The mean weighted percentage of AW/ASL varied markedly between centers as shown by the 31% SD and by the great heterogeneity between centers with some totally AW oriented (up to 100%) and other almost totally ASL oriented (up to 92%) (Table 2). Four centers (918 patients) specified tumor subtypes that were treated with AW and ASL. Among these centers 86% of the AW procedures and the 40% of the ASL procedures were performed for resection of infiltrative gliomas; the difference between the proportions was statistically significant ($p < 0.001$).

Parameters and settings of intraoperative stimulation

Cortical mapping was performed using bipolar Penfield direct electrostimulation in all centers, with 5 centers also using the monopolar short train direct electrostimulation. Subcortical mapping was performed using direct electrostimulation in 12 centers, using only monopolar direct electrostimulation in 3 centers, and using both techniques in 4 centers.

Table 2. Number of procedures in AW and ASL (some centers specified differences of indications for AW and ASL based upon pathologies)

Center	Awake surgeries (AW)	%	Asleep surgeries (ASL)	%	total
Almada	26	59%	18	41%	44
Barcelona	40	14.3%	240	85.7%	280
Berlin	62	21.7%	224	78.3%	286
Bern	45	7.7%	543	92.3%	
	AW for gliomas: 32 AW for gliomas: 13		ASL for gliomas 201 ASL for other lesions 342		588
Brescia	78	87.6%	11	12.4%	
	AW for gliomas: 70 AW for other lesions: 8		ASL for gliomas: 11 ASL for other lesions:0		89
Ferrara	35	64.8%	19	35.2%	54
Innsbruck	20	33.3%	40	66.7%	60
Lariboisiere Paris	33	86.8%	5	13.2%	38
Madrid	52	92.9%	4	7.1%	56
Nice	91	85%	16	15%	107
Poitiers	138	100%	0	0%	
	AW for gliomas: 117 AW for other lesions: 21		ASL for gliomas: 0 ASL for other lesions: 0		138
Thessaloniki	40	40%	60	60%	100
Santander	38	57.6%	28	42.4%	66
St. Anne Paris	70	74.5%	24	25.5%	
	AW for gliomas: 67 AW for other lesions: 3		ASL for gliomas: 20 ASL for other lesions: 4		94
Tilburg	95	96.9%	3	3.1%	
	AW for gliomas: 94 AW for other lesions: 1 Total AW for gliomas: 285 (86,4%) Total AW for other lesions: 46 (13,6%)		ASL for gliomas: 3 ASL for other lesions: 0 Total ASL for gliomas: 232 (40%) Total ALS for other lesions: 346 (60%)		98
	Total AW	863 (41.1%)	Total ASL (58.8%)	1235	2098

For AW, the parameters of stimulation for direct mapping were as follows: 11 centers (73%) used the same bipolar parameters for both motor and cognitive mappings (50-60 Hz, biphasic current, 0.5-1.0 ms), varying only the length of the stimulus (2-3 seconds for motor and 3-5 seconds for cognitive); 1 center (7%) used the same parameters for both motor and cognitive mappings, but used a monophasic current; 3 centers (20%) used different parameters for motor mapping (250 Hz, monophasic current, 0.5 ms, train of 5 or 4) and cognitive mapping (50-60 Hz, biphasic current, 0.2-1.0 ms); one of these centers used monophasic current also for cognitive mapping (Table 3).

The functional effects of direct electrostimulation during AS were observed by the neurosurgeon (26.6%), the anesthesiologist (20%), neuropsychologist or speech therapist (84%), neurophysiologist (33.3%) or others investigators (20%). The electrophysiologial effects of direct electrostimulation during AS were recorded at 39.9% centers (using ECoG in 33.3% and using EEG in 6.6%). For ASL the person who reports effect of stimulation was the neurosurgeon (20%), anesthesiologist (46.6%), neurophysiologist (46.6%) or other persons (20%). ECoG or EEG were used in 53.3% of centers (33.3% and 20% respectively) (tables 4 and 5).

Anesthesia protocol during AW

*A*nesthesia was performed using an Awake-Awake-Awake (AAA) protocol (i.e., using only scalp block and no intravenous drugs) in 20% of centers, whereas 79.9% preferred a aSleep-Awake-aSleep (SAS) protocol (i.e., using scalp block, sedation, awakening, and resedation). In the SAS protocol, the sedative medications were administered intravenously, and a laryngeal mask was applied in 33% of centers. The most commonly used drugs were propofol and remifentanyl (85.7%; Table 6).

Intraoperative seizure occurrence

IS had different characteristics in AW procedures (focal: 33.3%, generalized: 13.3%, both: 53.3%) and ASL

Table 3. Differences in intraoperative mapping parameters

CENTER	Type of cortical stimulation		Type of subcortical stimulation		Bipolar stimulation parameters (frequency/current/pulse duration)
	Bipolar	Monopolar	Bipolar	Monopolar	
Almada	1	1	1	1	60Hz, monophasic, 0.5ms
Barcelona	1	1	0	1	Motor: 250 Hz, 0.5ms, train of 5, max 20mA Cognitive: 50Hz, bifasic, 0.2ms, 3s based on the afterdischarge (no more then 15mA)
Berlin	1	1	1	1	60Hz, biphasic, 2-4s, max 12mA (until 2012: 52 cases with max 25mA)
Bern	1	1	1	1	Motor: 250 Hz, train of 5, monophasic, 0.5ms Cognitive: 50-60Hz, biphasic, 0.5-1ms
Brescia	1	0	1	0	Motor: 250Hz, monophasic, 0.1ms, train of 4 Cognitive: 60 Hz, biphasic, 0.5ms-1ms
Ferrara	1	0	0	1	Motor: 60 Hz, 0.2-0.5ms, 1,5-2s, 1.5-6mA Cognitive: 60Hz, 0.5ms, 2-4s, 5-15mA
Innsbruck	1	0	1	0	60 Hz biphasic, 1ms
Lariboisiere Paris	1	0	1	0	60Hz, biphasic, 0.5ms
Madrid	1	0	1	0	60Hz, bifphasic 2ms
Nice	1	0	1	0	60Hz, biphasic, 1ms
Poitiers	1	0	1	0	60Hz, biphsic, 1ms
Thessaloniki	1	0	0	1	60Hz, biphasic, 0.5ms , train of 5
Santander	1	0	1	0	60Hz, biphasic, 1ms, train of 4
St. Anne Paris	1	0	1	0	60Hz, biphasic, 0,5ms, train of 5
Tilburg	1	1	1	1	60Hz, biphasic, 0.5-1ms
	Only bipolar 10 (66.6%)	both 5 (31.25%)	only bipolar 8 (53.3%)	only monopolar 3 (20%) both 4 (26.6%)	

procedures (focal: 8.3%, generalized: 42.8%, both: 33.3%), The difference between the groups was not statistically significant ($p = 0.06$). There were significantly more patients presenting with preoperative seizures in the AW group ($n = 645$, 77.4%) than in the ASL group ($n = 566$, 45.8%) ($p < 0.001$). Significantly more patients had IS in the AW group ($n = 155$; 18.6%, range 2.9%-54.3%) than in the ASL group ($n = 109$; 8.8%, range 0%-100% ($p < 0.001$). There was significant difference between centers in the occurrence of IS in AW patients ($p < 0.001$) (Table 7). We compared centers on the basis of their specialization: centers performing more AW than ASL reported more IS in their ASL patients ($z = 7.8$), while centers performing more ASL than AW reported more IS in their AW patients ($z = 4.8$).

We checked for a possible association between preoperative seizures and IS. The two event are not independent as tested by $p(pre)p(intra) \neq p(pre \text{ AND } intra)$ with a binomial test ($p(a) = 60\%$, $p(b) = 6\%$, $p(pre \text{ AND } intra) = 8\%$, $p < 0.001$). Interestingly, in 9 cases (0.4%) IS occurred before the craniotomy.

Perioperative AED use

There appears to be a high percentage of patients with seizures at onset for both AS group and ASL group with also a wide range among centers (40% to 97.5% for AS groupand 16.7% until 100% for ASL group). For patients who were already on AEDs for preoperative seizures, 7 centers (46.6%) added another drug (levetiracetam [median dose 1000 mg] in 6 centers) and phenytoin [median dose 100 mg] in the remaining), while 2 centers (13.3%) increased the dose of the patient's AEDs (1 center before surgery and 1 center after surgery). For patients without history of preoperative seizures, AED prophylaxis was administered preoperatively in 75% of cases.

Table 4. Types of brain activity monitoring and personnel involved in intraoperative patient evaluation during AS

Center	Type of brain activity monitoring			Operating room attendant						
	ECoG	tcEEG	none	Surgeon	Anesthesiologist	Neurpsychologist	Speech therapist	Neurophysiologist	Other	number of staff controlling the stimulation's effects
Almada	0	0	1	0	0	1	0	0	1	2
Barcelona	1	0	0	0	0	1	0	1	0	2
Berlin	1	0	0	1	0	0	0	1	0	1
Bern	1	0	0	1	0	1	0	1	0	2
Brescia	0	1	0	0	1	1	0	0	0	2
Ferrara	1	0	0	0	0	1	0	0	0	1
Innsbruck	0	0	1	1	0	1	0	0	1 Not specified	2
Lariboisiere Paris	0	0	1	1	1	1	0	1	0	2
Madrid	0	0	1	0	0	1	1	0	0	2
Nice	0	0	1	0	1	0	1	0	0	2
Poitiers	0	0	1	0	0	1	1	0	1 Neurologist	3
Thessaloniki	1	0	0	0	1	0	0	0	1	
Santander	0	0	1	0	0	1	0	0	0	1
S t. Anne Paris	0	0	1	0	0	0	1	0	0	1
Tilburg	0	0	1	0	0	1	0	0	0	1
	533.3%	16.6%	96 0%	426.6%	320%	1280%	426.6%	533.3%	320%	

Levetiracetam (median dose 1000 mg) was the preferred drug in 68.7% of these patients (Table 8). However, the occurrence of IS was not significantly different between centers using or not using AED prophylaxis (12% vs. 12%; $p = 0.2$).

Characteristics of patients with IS during AW

Patients experiencing IS during AW had a mean age 44 ± 11 years at surgery. Both genders were similarly affected (57% males vs. 43% females; $p = 0.14$). Of those experiencing IS, 56% had WHO grade II gliomas, 24% had grade III gliomas, and 20% had grade IV gliomas; the higher occurrence associated with grade II tumors was statistically significant. IS was seen in 64% of patients with left-sided gliomas and 36% of those with right-sided gliomas; the higher propensity for IS in the former was also statistically significant ($p < 0.01$) The tumor was located in the frontal lobe in 25% of patients, the primary motor cortex in 22%, the supplementary motor cortex in 13%, the insular lobe in 16%, the temporal lobe in 17%, and the parietoocipital lobe in 7%; the differences were statistically significant (p for chi-square = 0.007).

Discussion

Choice of AW or ASL

Our data showed that centers tend to prefer one mapping technique over the other and, accordingly, we divided the 15 centers into two broad categories that we term "Awakers" (those who prefer AW) and "Asleepers" (those who prefer ASL). However, all the center but one perform both techniques. This finding was interesting, as those using predominantly ASL are supposed to exclude patients harboring a glioma in language areas, since no language testing is possible in an asleep patient. A possible explanation could be that the expertise and accumulated experience of a center in one or the other technique lead consequently to a selection of patients and pathologies. However, excellent results have been reported about the efficacy of monitoring and mapping during resection of motor area tumors in anesthetized patients [21–24]. From subgroup analyses based upon histology (data available from only 4 centers—accounting for more than 900 patients), it was obvious that AW was the preferred technique for gliomas, owing to their infiltrative growth pattern [25].

The risk of IS during glioma resection under intraoperative functional mapping is directly linked to the concept of direct electrostimulation, as tumor infiltration by

Table 5. Types of brain activity monitoring and personnel involved in intraoperative patient evaluation during ASL

Center	Type of brain activity monitoring			Operating room attendant						
	ECoG	tcEEG	none	Surgeon	Anesthesiologist	Neurpsychologist	Speech therapist	Neurophysiologist	Other	number of staff controlling the stimulation's effects*
Almada	0	1	0	0	0	0	0	1	0	1
Barcelona	1	0	0	0	0	0	0	1	0	1
Berlin	0	0	1	1	0	0	0	0	0	0
Bern	1	1	0	1	0	0	0	1	0	1
Brescia	0	1	0	0	1	0	0	1	0	2
Ferrara	1	0	0	0	0	0	0	1	0	1
Innsbruck	0	0	1	1	0	0	0	0	1 Not specified	1
Lariboisiere Paris	0	0	1	0	1	0	0	0	0	1
Madrid	0	0	1	0	1	0	0	0	0	1
Nice	0	0	1	0	1	0	0	0	0	1
Poitiers	0	0	0	0	1	0	0	0	0	1
Thessaloniki	1	0	0	0	0	0	1	0	1	
Santander	1	0	0	0	1	0	0	0	0	1
St. Anne Paris	0	0	1	0	1	0	0	0	0	1
Tilburg	0	0	1	0	0	0	0	1	0	1
	33.3%	320%	746.6%	320%	746.6%	0	0	746.6%	320%	

* Except the surgeon

gliomas can involve the brain parenchyma in eloquent areas. It is known that the infiltrated neocortex contains epileptic foci that can be excited through direct electrostimulation [26].

The occurrence of IS during intraoperative mapping is an important issue not only because it affects the patient's safety during surgery but also because it prevents completion of a satisfactory functional cortical and subcortical mapping, which is essential for the subsequent resection The average rate of IS in the present survey was consistent with previous reports, although we did observe wide variation of IS incidence between centers (2.9% to 54.3% in AW and 0% to 100% in ASL) [10]. This finding raises questions regarding consistency in the definition of IS and the methods used to detect them. The relatively low frequency of the use of ECoG and EEG (40% during AS, 53.3% during ASL) and the fact that not all the centers rely on the presence of a dedicate person into the operating room, makes possible that either subclinical epileptiform activity or subtle clinical seizures were underestimated. Concerning the former, it could be argued that intraoperative EEG alterations should not be defined as seizures.

It appears that the IS rate depends on the relative expertise of the center in AW and ASL, as the "Awakers" centers have lower rates of IS during AW than during ASL, while the "Asleepers" centers have lower rates of IS during ASL than during AW. More, it can be argued that these two procedures hold peculiarities and differences which must be recognized and specific training in one or another should be favored. However, these are the results of the surgery that possibly did not detect other possible factors that could explain such discrepancies.

Although the IS rate in the AW group is almost double that in the ASL group (18.6% vs. 8.8%), the design of our survey does not allow us to draw any conclusions, considering that the ASL group also includes patients undergoing intraoperative monitoring with no direct electrostimulation.

Several authors have published their experience about IS during AW and, the results have been inconsistent. Nossek et al. [9] observed an incidence of IS during AW of 12.6%; Deras et al. reported [14] no occurrence of IS in a recent series of 140 awake craniotomies; and Boetto et al. [19] reported an incidence of IS during AW of 3.4% in a prospective analysis of 374 patients.

Table 6. Type of anesthesia protocol. AAA, awake-awake-awake (only scalp block and no intravenous drugs). SAS (scalpblock, intravenous sedation, awakening, re-sedation). SAS 2 (scalp block, laryngeal mask, awakening, laryngeal mask). ND: not determined

Center	Anesthesiology protocol			Drugs		
	AAA	SAS	SAS2	Propophol	Remifentanil	Dexmedetomidine
Almada	0	0	1	1	1	0
Barcelona	1	0	0	1	1	0
Berlin	0	1	0	1	1	0
Bern	0	0	1	0	1	0
Brescia	1	0	0	1	1	0
Ferrara	0	1	0	1	1	0
Innsbruck	0	1	0	1	1	0
Lariboisiere Paris	0	1	0	1	1	0
Madrid	1	0	0	1	1	0
Nice	0	0	1	1	1	0
Poitiers	0	1	0	ND	ND	ND
Thessaloniki	0	1	0	1	1	0
Santander	0	0	1	0	0	1
St. Anne Paris	0	0	1	1	1	0
Tilburg	0	1	0	1	1	0
	3/15 (20%)	7/15(46,6%)	5/15 (33,3%)	Propofol+Remifentanil 12/14 (85.7%) Remifentanil 1/14 (7.1%) Dexmedetomidine 1/14 (7.1%)		

Several methods have been proposed to reduce the rate of IS. The train-of-five technique seems to be associated with a low rate of IS (1.2% vs. 9.5% with the 60-Hz technique). [10] The data from our study shows that 75% of centers use a classical bipolar direct electrostimulation technique (50-60 Hz, biphasic current, 0.5-1 ms) for both motor and cognitive mappings. Evidently, there are other factors involved in the occurrence of IS, such as the surgeon's experience in the procedure. As pointed out by Szelényi et al. [10], the current intensity and length of its application to the cortical site, as well as the interval between repeated stimuli at the same cortical site, can strongly account for the onset of IS. Recently, Karakis et al. [27] demonstrated that longer stimuli and higher current intensity correlate with intrastimulation discharges, which in turn facilitate the appearance of afterdischarges and IS. The group from Montpellier [19] underline the importance of systematically stimulating the sensory-motor area at the beginning of the mapping to identify the lowest current intensity providing reproducible positive responses; this can then be used for the entire mapping procedure Some authors have also implicated the anesthetic regimen in the occurrence of IS. For example, higher intensity of electrostimulation is required in patients anesthetized with sevoflurane than in those who have received propofol, so the likelihood of IS with the former is greater [2]. In our sample, a high proportion (80%) used the combination of propofol and remiphentanyl for SAS.

Preoperative seizures

Globally, there was high frequency of patients suffering from seizures at onset and also high variability in rates among centers. This variability is difficult to explain as it could depend on the difference in treated pathology, on the degree of seizure control under antiepileptic drug therapy, on the severity or frequency of seizures.

Our data support the possibility that having seizures preoperatively can somehow increase the risk of IS occurrence. Moreover, the risk of IS is higher with WHO grade II glioma (which are known to be highly epileptogenic tumors). In our sample, the risk of IS was two-fold higher in patients with grade II glioma than in patients with high grade glioma. Possibly the increased risk of IS we observed in the AW group was due to the high proportion of patients who already had a greater risk of seizure.

Our findings are only partially consistent with the previous literature. According to some authors [10], IS occurrence is similar in patients with history of preoperative seizures (2%) and in those without seizure history (0.7%). Other authors, however, have found that patients who suffered from preoperative seizures and harbored a LGG were more prone to have

Table 7. Frequencies of preoperative and intraoperative seizures and type of IS between AS and ASL

Center	Awake surgery (863 patients)				Asleep surgery (1235 patients)				Patients with seizures pre and intraoperatively
	Preop seizures	IS	Type		Preop seizures	IS	Type		
			Focal	Gener			Focal	Gener	
Almada	14 (53.9%)	7 (27%)	1	1	7 (39%)	3 (16.7%)	0	1	10 (100%)
Barcelona	36 (90%)	6 (15%)	1	1	96 (40%)	12 (5%)	0	1	16 (88.9)
Berlin	37 (59.6%)	19 (31%)	1	1	64 (28,6%)	2 (0,9%)	0	1	21 (100%)
Bern	27 (60%)	2 (4.4%)	0	1	244 (45%)	22 (4%)	1	0	16 (66.7%)
Brescia	44 (56.4%)	7 (9%)	1	0	4 (36.4%)	7 (63.6%)	0	1	9 (64.3%)
Ferrara	26 (74.2%)	19 (54,3%)	1	1	13 (72.2%)	0 (0%)	0	0	12 (63.2%)
Innsbruck	8 (40%)	2 (10%)	0	1	21 (52.5%)	7 (17.5%)	1	1	8 (88.9%)
Lariboisiere Paris	26 (78.8%)	2 (6%)	1	0	4 (80%)	5 (100%)	0	1	0 (0%)
Madrid	48 (92.3%)	10 (19.2%)	1	0	4 (100%)	4 (100%)	1	1	14 (100%)
Nice	80 (87.9%)	8 (8.8%)	1	0	13 (81.2%)	12 (75%)	1	1	20 (100%)
Poitiers	107 (77.5%)	56 (40.6%)	1	1	NP	NP	NP	NP	48 (85.7%)
Thessaloniki	39 (97.5%)	3 (7.5%)	1	1	60 (100%)	2 (3,3%)	1	1	5 (100%)
Santander	25 (65.8%)	5 (13.2%)	1	1	15 (53.6%)	20 (71.4%)	1	1	NR
St. Anne Paris	52 (74.3%)	2 (2.9%)	1	0	18 (75%)	12 (50%)	0	1	9 (64.3%)
Tilburg	76 (80%)	8 (8,4%)	1	1	3 (100%)	0 (0%)	0	0	5 (62.5%)
Total	645 (74.7%) range 40-97.5%	161 (18.6 %) range 2.9-54.3%	5/15 (33,3%) Both 8/15 (53.3%)	2/15 (13.3%)	566 (45.8%) Range 16.7-100%	108 (8.8%) range 0-100%	1/14 (7.1%) Both 5/14 (35.7%)	6/14 (42.8%)	193 (73.9%)

Table 8. Perioperative management of AEDs in patients with and without seizures at onset (LVT: levetiracetam; PHN: phenitoyn)

Center	Patients with seizures already on AED						Patients without seizures			
	Add on New AED	unchanged therapy	Epileptologic evaluation	LVT	PHN	Daily dose (mg)	AED prophyl axis	LVT	PHN	Daily dosage (mg)
Almada	1	0	0	1	0	1000	1	1	0	1000
Barcelona	1	0	0	1	0	1000	1	1	0	1000
Berlin	0	1	0	0	0	0	0	0	0	0
Bern*	1	0	0	1	0	1000	1	1	0	1000
Brescia	1	0	0	1	0	1000	1	1	0	1000
Ferrara	0	1	0	0	0	0	0	0	0	0
Innsbruck	0	1	0	0	0	0	0	0	0	0
Lariboisiere Paris**	0	0	0	0	0	0	1	1	0	1000
Madrid	0	1	0	0	0	0	0	0	0	2000
Nice	0	1	0	0	0	0	1	1	0	1000
Poitiers	0	0	1	0	0	0	1	1	0	1000
Thessaloniki	1	0	0	1	0	1000	1	1	0	1000
Santander	0	1	0	0	0	0	1	1	0	2000
St. Anne Paris	1	0	0	1	0	500	1	1	0	500
Tilburg	1	0	0	0	1	500	1	0	1	500
	7 (46.6%)	6 (40%)	1 (6.6%)	6/7 (85.7%)	1/7 (14,2%)		1 1 (73.3%)	10/11 (90.9%)	1/11 (9%)	

* increase the dose preoperatively

* * increase the dose postoperatively

IS during the mapping procedure [28]. One large series that only included LGG patients reported correlation between preoperative seizures and the risk of developing IS [19]. It is worth noting that the majority of AW and direct mapping are performed for tumors in the left hemisphere; whether to awaken the patient for a tumor in the right hemisphere (other than in the sensory area) is still undecided. Therefore, the preponderance of left-side tumors in this study may have introduced a selection bias.

AED prophylaxis

Several meta-analyses have found that there is no evidence to support the practice of using AED to prevent postoperative seizures. However, no guidelines are available regarding the use of AED prophylaxis. A consensus statement issued by the Quality Standards Subcommittee of the American Academy of Neurology discourages routine use of AED prophylaxis in patients with brain tumors and recommends that these drugs be withdrawn within the first week after surgery if patients are still seizure free [28]. Yet, despite the evidence [29], according to the survey conducted by Siomin et al. [30], over 70% of polled neurosurgeons regularly use AED prophylaxis for resection of gliomas or metastases. De Groot et al. [31] hypothesized that AEDs fail to prevent seizures in patients with brain tumors because most AED block excitatory mechanisms, whereas seizures in tumor patients may be the consequence of multifactorial mechanisms [32]. It is also possible that failure to achieve the optimal serum levels is the reason for the poor prophylactic effect [31]. Many surgeons consider that the direct stimulation itself may be the cause of IS and postoperative seizures, and hence many are in favor of AED administration. These uncertainties are reflected in the lack of uniformity in the use of AED prophylaxis In those patients already on AEDs, nearly 60% of the centers modified therapy, either by adding a new drug or by increasing the dose of the patient's current drug. More interestingly, 73.3% of centers initiated AED therapy preoperatively in patients without history of seizures.

On examining the different subtypes of IS in our survey data, it is clear that simple partial seizures are common during AW, whereas generalized seizures predominate in ASL ($p = 0.049$). In our study, levetiracetam was the most favored drug for glioma-related seizures, but it should be underlined that this molecule is not the gold standard for treatment of partial simple seizure. One could argue that other AEDs should be preferred for perioperative prophylaxis during AW.

Limitations

The reported variability among centers regarding some data (i.e. IS rate, preoperative seizures rate etc.) may be a limitation in the interpretation of results. In general, the survey design shows advantages and limitations. The main limitation is that respondents may not be fully aware of their reasons for any given answer because of lack of memory on the subject or because their personal database is not accurate enough on a specific topic. In that sense, some form of reporting bias should be considered. Moreover, data deriving from a survey could be insufficient in detecting substantial factors which are multiple intermixed and would require deeper analyses and, basically, a different study design.

Indeed, when speaking about the need of perioperative AED prophylaxis, we must underline that some confounding factor can be recognize such as the sample size difference (1698 patients with prophylaxis, 400 without); the number of AW procedures in patients with prophylaxis (44%) vs. without (29%).

Conclusions

This is the first European survey to assess intraoperative functional mapping and monitoring protocols and the management of peri- and intraoperative seizures from a large sample of patients. Although the design of this survey does not allow us to draw definite conclusions, we have collected useful data about the prevailing situation in centers treating eloquent area tumors. This information should be valuable for identifying specific issues that need to be investigated in future prospective and controlled studies.

Acknowledgments Pasquale DE BONIS thanks Giulia Ghisellini (medical student) for the data collection.

Johan PALLUD thanks Edouard Dezamis, Marc Zanello (neurosurgeons) and Odile Rigau-Viodé (speech therapist).

Giannantonio SPENA thanks Pier Paolo Panciani (neurosurgeon) for the intellectual support.

References

1. De Witt Hamer PC, Robles SG, Zwinderman AH, Duffau H, Berger MS (2012) Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. J Clin Oncol. 30(20): 2559–2565
2. Duffau H (2015) Resecting diffuse low-grade gliomas to the boundaries of brain functions: a new concept in surgical neuro-oncology. J Neurosurg Sci. 59(4):361–371
3. Spena G, Panciani PP, Fontanella MM (2015) Resection of supratentorial gliomas: the need to merge microsurgical technical cornerstones with modern functional mapping concepts. An overview. Neurosurg Rev. 38(1):59–70
4. Penfield W, Boldrey E (1937) Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain 60:389–443
5. Taniguchi M, Cedzich C, Schramm J (1993) Modification of cortical stimulation for motor evoked potentials under general anesthesia: Technical description. Neurosurg. 32:219–226
6. Kombos T, Suess O, Funk T, Kern BC, Brock M (2000) Intraoperative mapping of the motor cortex during surgery in and around the motor cortex. Acta Neurochir 142(3):263–268
7. Szelényi A, Kothbauer KF, Deletis V (2007) Transcranial electric stimulation for intraoperative motor evoked potential monitoring: Stimulation parameters and electrode montages. Clin Neurophysiol. 118(7):1586–1595
8. Cordella R, Acerbi F, Marras CE, Carozzi C, Vailati D, Saini M, Tringali G, Ferroli P, Dimeco F, Franzini A, Broggi G (2013) Risk of seizures during intraoperative electrocortical stimulation of brain motor areas: a retrospective study on 50 patients. Neurol Sci. 34(1):63–70
9. Nossek E, Matot I, Shahar T, Barzilai O, Rapoport Y, Gonen T, Sela G, Grossman R, Korn A, Hayat D, Ram Z (2013) Intraoperative seizures during awake craniotomy: incidence and consequences: analysis of 477 patients. Neurosurg. 73(1):135–140
10. Szelényi A, Joksimovič B, Seifert V (2007) Intraoperative risk of seizures associated with transient direct cortical stimulation in patients with symptomatic epilepsy. J Clin Neurophysiol 24:39–43
11. Gupta DK, Chandra PS, Ojha BK, Sharma BS, Mahapatra AK, Mehta VS (2007) Awake craniotomy versus surgery under general anesthesia for resection of intrinsic lesions of eloquent cortex–a prospective randomised study. Clin Neurol Neurosurg 109(4):335–343
12. Kim SS, McCutcheon IE, Suki D, Weinberg JS, Sawaya R, Lang FF, Ferson D, Heimberger AB, DeMonte F, Prabhu SS (2009) Awake craniotomy for brain tumors near eloquent cortex: correlation of intraoperative cortical mapping with neurological outcomes in 309 consecutive patients. Neurosurg. 64(5):836–845
13. Sacko O, Lauwers-Cances V, Brauge D, Sesay M, Brenner A, Roux FE (2011) Awake craniotomy vs surgery under general anesthesia for resection of supratentorial lesions. Neurosurg. 68(5):1192–1198
14. Deras P, Moulinié G, Maldonado IL, Moritz-Gasser S, Duffau H, Bertram L (2012) Intermittent general anaesthesia with controlled ventilation for asleep-awake-asleep brain surgery: a prospective series of 140 gliomas in eloquent areas. Neurosurg. 71:764–771
15. Chacko AG, Thomas SG, Babu KS, Daniel RT, Chacko G, Prabhu K, Cherian V, Korula G (2013) Awake craniotomy and electrophysiological mapping for eloquent area tumours. Clin Neurol Neurosurg. 115(3):329–324
16. Grossman R, Nossek E, Sitt R, Hayat D, Shahar T, Barzilai O, Gonen T, Korn A, Sela G, Ram Z (2013) Outcome of elderly patients undergoing awake-craniotomy for tumor resection. Ann Surg Oncol. 20(5):1722–1728
17. Spena G, D'Agata F, Panciani PP, Buglione di Monale M, Fontanella MM (2013) Supratentorial gliomas in eloquent areas: which parameters can predict functional outcome and extent of resection? PLoS One. 8(12):e80916
18. Beez T, Boge K, Wager M, Whittle I, Fontaine D, Spena G, Braun S, Szelényi A, Bello L, Duffau H, Sabel M (2013) European Low Grade Glioma Network. Tolerance of awake surgery for glioma: a prospective European Low Grade Glioma Network multicenter study. Acta Neurochir. 155(7):1301–1308
19. Boetto J, Bertram L, Moulinié G, Herbet G, Moritz-Gasser S, Duffau H (2015) Low rate of intraoperative seizures during awake craniotomy in a prospective cohort with 374 supratentorial brain

lesions: electrocorticography is not mandatory. World Neurosurg. 84(6):1838–1844
20. Hervey-Jumper SL, Li J, Lau D, Molinaro AM, Perry DW, Meng L, Berger MS (2015) Awake craniotomy to maximize glioma resection: methods and technical nuances over a 27-year period. J Neurosurg. 123(2):325–339
21. Mehta V, Danks RA, Black PM (2000) Cortical mapping under local anaesthesia for tumor resection. Seminars in Neurosurg 11: 287–299
22. Sala F, Lanteri P (2003) Brain surgery in motor areas: the invaluable assistance of intraoperative neurophysiological monitoring. J Neurosurg Sci. 47(2):79–88
23. Romstöck J, Fahlbusch R, Ganslandt O, Nimsky C, Strauss C (2002) Localisation of the sensorimotor cortex during surgery for brain tumours: feasibility and waveform patterns of somatosensory evoked potentials. J Neurol Neurosurg Psych. 72(2):221–229
24. Neuloh G, Pechstein U, Cedzich C, Schramm J (2004) Motor evoked potential monitoring with supratentorial surgery. Neurosurgery. 54(5):1061–1070
25. Pallud J, Varlet P, Devaux B, Geha S, Badoual M, Deroulers C, Page P, Dezamis E, Daumas-Duport C, Roux FX (2010) Diffuse low-grade oligodendrogliomas extend beyond MRI-defined abnormalities. Neurology. 74(21):1724–1731
26. Pallud J, Le Van Quyen M, Bielle F, Pellegrino C, Varlet P, Labussiere M, Cresto N, Dieme MJ, Baulac M, Duyckaerts C, Kourdougli N, Chazal G, Devaux B, Rivera C, Miles R, Capelle L, Huberfeld G (2014) Cortical GABAergic excitation contributes to epileptic activities around human glioma. Sci Transl Med 6(244):244ra89
27. Karakis I, Leeman-Markowski BA, Leveroni CL, Kilbride RD, Cash SS, Eskandar EN, Simon MV (2015) Intra-stimulation discharges: An overlooked cortical electrographic entity triggered by direct electrical stimulation. Clinical Neurophys 126:882–888
28. Glantz MJ, Cole BF, Forsyth PA, Recht LD, Wen PY, Chamberlain MC, Grossman SA, Cairncross JG (2000) Pratice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 54(10):1886–1893
29. Sayegh ET, Fakurnejad S, Oh T, Bloch O, Parsa AT (2014) Anticonvulsant prophylaxis for brain tumor surgery: determining the current best available evidence. J Neurosurg 121:1139–1147
30. Siomin V, Angelov L, Li L, Vogelbaum M (2005) Results of a survey of neurosurgical practice patterns regarding the prophylactic use of anti-epilepsy drugs in patients with brain tumors. J Neuro-Oncol 74:211–215
31. de Groot M, Reijneveld JC, Aronica E, Heimans JJ (2012) Epilepsy in patients with a brain tumour: focal epilepsy requires focused treatment. Brain. 135(Pt 4):1002–1016
32. Pallud J, Capelle L, Huberfeld G (2013) Tumoral epileptogenicity: how does it happen? Epilepsia. 54(Suppl 9):30–34