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ORIGINAL ARTICLE

Is function-based resection using intraoperative awake brain mapping feasible and safe for solitary brain metastases within eloquent areas?

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Abstract

To assess feasibility and safety of function-based resection under awake conditions for solitary brain metastasis patients. Retrospective, observational, single-institution case-control study (2014-2019). Inclusion criteria are adult patients, solitary brain metastasis, supratentorial location within eloquent areas, and function-based awake resection. Case matching (1:1) criteria between metastasis group and control group (high-grade gliomas) are sex, tumor location, tumor volume, preoperative Karnofsky Performance Status score, age, and educational level. Twenty patients were included. Intraoperatively, all patients were cooperative; no obstacles precluded the procedure from being performed. A positive functional mapping was achieved at both cortical and subcortical levels, allowing for a function-based resection in all patients. The case-matched analysis showed that intraoperative and postoperative events were similar, except for a shorter duration of the surgery ($p<0.001$) and of the awake phase ($p<0.001$) in the metastasis group. A total resection was performed in 18 cases (90%, including 10 supramarginal resections), and a partial resection was performed in two cases (10%). At three months postoperative months, none of the patients had worsening of their neurological condition or uncontrolled seizures, three patients had an improvement in their seizure control, and seven patients had a Karnofsky Performance Status score increase ≥10 points. Function-based resection under awake conditions preserving the brain connectivity is feasible and safe in the specific population of solitary brain metastasis patients and allows for high resection rates within eloquent brain areas while preserving the overall and neurological condition of the patients. Awake craniotomy should be considered to optimize outcomes in brain metastases in eloquent areas.

Keywords Awake surgery · Brain metastasis · Extent of resection · Feasibility · Intraoperative brain mapping · Safety

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Introduction

The surgical resection of brain metastases aims to (1) provide the histo-molecular diagnosis and/or characterize a molecular anomaly for a targeted therapy [11]; (2) discriminate between radiation-induced changes (the so-called radionecrosis) and tumor recurrence in cases of previous radiotherapy [26]; (3) reduce symptoms of intracranial hypertension, focal neurological deficits, and seizures, and allow for a rapid steroid taper [25]; and (4) improve local tumor control and overall survival in case of a solitary metastasis, particularly in the setting of a large tumor, a cystic or necrotic tumor, and/or a cortico-subcortical tumor topography considering the low efficacy and potential adverse effects of stereotactic radiotherapy in these situations [11].

The surgical resection of brain metastases located in eloquent areas remains a particular challenge due to the higher risk of postoperative neurological and neurocognitive deficits [4, 21]. It is a crucial issue since survival is linked to both the extent of resection and the functional status of the patient [21]. Intraoperative functional brain mapping under awake surgery [5, 6, 12, 14, 20] has potential advantages: (1) safe approach to the metastasis through the identification of eloquent cortico-subcortical connectivity [7, 17], (2) resection according to functional connectivity and beyond the limits of the metastasis [10], and (3) better control of the surgical risks regarding metastases initially deemed inoperable and previously treated with stereotactic radiotherapy for which a histo-molecular diagnosis is required. Previous series have reported awake surgery for brain metastases [7, 9, 10, 21]. Two pioneer studies from Dusseldorf reported that awake surgery is feasible for metastases in eloquent areas, minimizing postoperative neurologic deficits and morbidity and permitting supramarginal resection [9,

Table 1 Metastasis and control group paired by matching criteria

Patient	Metastasis group							Control group						
	Age (year)	Lobe	Side	Volume (cm^3)	KPS Score	Sex	Education level	Age (year)	Lobe	Side	Volume (cm^3)	KPS score	Sex	Education level
Complete match														
20	43	P	L	4.2	80	M	7	42	P	L	2.0	90	M	7
7	43	P	L	7.4	80	F	7	40	P	L	11.6	80	F	7
17	52	T	L	6.2	90	F	4	47	T	L	3.1	90	F	4
2	58	F	L	12.1	80	F	7	63	F	L	14.6	90	F	7
4	64	F	L	36.7	100	F	7	62	F	L	20.8	80	F	7
18	64	F	R	16.3	90	M	7	68	F	R	22.9	90	M	7
9	46	T	L	160.0	70	F	7	43	T	L	135.5*	70	F	7
Incomplete match in one criterion£														
6	50	F	R	27.0	90	M	**7**	54	F	R	28.8	80	M	**5**
13	50	F	R	1.4	90	M	**4**	46	F	R	0.7	100	M	**3**
3	50	T	L	45.4	70	M	**4**	55	T	L	44.8	80	M	**7**
14	62	T	L	9.6	100	M	**7**	59	T	L	10.0	100	M	**4**
15	64	F	R	2.0	90	F	**7**	65	F	R	3.1	100	F	**4**
8	69	F	R	20.9	70	M	**4**	65	F	R	24.5*	80	M	**6**
1	49	F	L	**31.7**	90	M	7	40	F	L	**81.3**	80	M	7
19	35	T	L	7.5	**90**	F	6	33	T	L	10.8	**50**	F	6
5	44	F	L	33.1	**80**	M	7	46	F	L	36.9	**60**	M	7
11	74	F	L	3.8	**60**	M	7	74	F	L	8.0	**100**	M	7
Incomplete match in two criteria£														
16	65	T	L	4.9	70	**F**	**7**	62	T	L	7.9	80	**M**	**6**
10	48	T	L	106.0	**70**	M	**7**	51	T	L	98.0*	**100**	M	**6**
12	78	P	L	17.6	90	**M**	**6**	80	P	L	24.3	100	**F**	**5**

Lobe: *F* frontal, *P* parietal, *T* temporal; Side: *L* left, *R* right; Sex: *F* female, *KPS* Karnofsky Performance Status, *M* male

£ Imperfectly matched criteria are shown in bold type

*No contrast enhancement, tumor volume on Fluid Attenuated Inversion Recovery sequence

Table 2 Characteristics of the patients under study

Parameters		Metastasis group		Control group		*p* value
		n	%	*n*	%	
Sex	Male	12	60	11	55	0.589
	Female	8	40	9	45	
Age (year)	Mean ± SD (range)	55.6 ± 11.4		55.8 ± 11.8		0.924
Oncological treatment before surgery	No	6	30	17	85	**<0.001**
	Yes	14	70	3	15	
	Previous surgery of the lesion	2		1		
	Radiotherapy	10		2		
	Stereotactic radiotherapy	8				
	Conformational radiotherapy			2		
	Whole brain radiotherapy	2				
	Chemotherapy	12		1		
Increased intracranial pressure	No	19	95	19	95	1.0
	Yes	1	5	1	5	
Focal neurological deficit	No	9	45	11	55	0.527
	Yes	11	55	9	45	
	Weakness/paresis	4				
	Language disturbances	6				
	Sensory disturbances	1				
Cognitive evaluation	No	2	10	1	5	0.545
	Yes	18	90	19	95	
Cognitive deficit*	No	4	20	3	15	0.617
	Yes	14	70	16	80	
	Not evaluated	2	10	1	5	
Epileptic seizure	No	10	50	3	15	**0.016**
	Yes	10	50	17	85	
Seizure control£	No	3	30	4	23.5	0.589
	Yes	7	70	17	76.5	
KPS score	Mean ± SD (range)	81.5 ± 16.4		81.5 ± 10.4		0.232
	70 and >	19	95	17	85	0.292
	< 70	1	5	3	15	
Main lobar location	Frontal	10	50	11	55	0.875
	Temporal	7	35	7	35	
	Parietal	3	15	2	10	
Side	Left	15	75	15	75	1.0
	Right	5	25	5	25	
Tumor volume (cm^3)	Mean ± SD (range)	21.9 ± 40.7		21.7 ± 20.0		0.107
Histopathology	Lung	8	40	11 IDH-wildtype glioblastomas		
	Melanoma	2	10	5 IDH-mutant grade 3 oligodendrogliomas		
	Gastrointestinal tract	1	5	2 IDH-mutant grade 3 astrocytomas		
	Kidney	1	5	2 IDH-mutant grade 4 astrocytomas		
	Breast	1	5			
	Perivascular epithelioid cell tumor	1	5			
	Testis non seminomatous germ cell tumor	1	5			
	Radionecrosis	5	25			
	Breast	3				
	Lung	2				
Extent of resection	Total (supramarginal)	18 (10)	90 (50)	15 (3)	75 (15)	**0.046**
	Partial	2	10	5	25	
Early clinical worsening	No	15	75	7	35	**0.010**

Table 2 (continued)

Parameters		Metastasis group		Control group		*p* value
		n	%	*n*	%	
	Yes	5	25	13	65	
Early postoperative seizure	No	18	90	19	95	0.548
	Yes	2	10	1	5	
Early postoperative KPS score	Mean ± SD (range)	76.5 ± 10.9		73.5 ± 11.4		0.330
	70 and >	18	90	16	80	0.376
	< 70	2	10	4	20	
Duration of hospital stay (day)	Mean ± SD (range)	20.0 ± 51.9		10.4 ± 4.8		0.118
Discharge	Home	18	90	13	65	0.058
	Institution	2	10	7	35	
Postoperative infection	No	18	90	20	100	0.148
	Yes	2	10	0	0	
Postoperative medical complication	No	17	85	18	90	0.633
	Yes	3	15	2	10	
Postoperative oncological treatment	No	4	20	0	0	**0.012**
	Yes	15	75	100	100	
	Death	1	5	0	0	
3-month postoperative clinical worsening	No	18	90	16	80	0.153
	Yes	0	0	4	20	
	Death	2	10	0	0	
3-month postoperative epileptic seizure	No	8	40	3	15	**0.031**
	Yes	10	50	17	85	
	Death	2	10	0	0	
3-month postoperative seizure control$	No	0	0	3	17.7	0.158
	Yes	10	100	17	82.3	
3-month postoperative KPS score	Mean ± SD (range)	86.0 ± 10.9		83.9 ± 15.4		0.915
	70 and more	15	75	19	95	0.117
	< 70	3	15	1	5	
	Death	2	10	0	0	
Cognitive evaluation	No	11	55	6	30	0.027
	Yes	9	45	14	70	

IDH isocitrate dehydrogenase, *KPS* Karnofsky Performance Status, *SD* standard deviation

[*] Cognitive deficits are detailed in Table 5

[£] In patients with seizures at the time of surgery

[$] In patients with seizures after surgery

10]. They suggested that awake craniotomy should be considered as a technique to optimize outcomes in brain metastases in eloquent areas.

The present study was aimed to find out whether patients harboring a solitary brain metastasis located in eloquent areas can be operated safely with the aid of awake surgery techniques. We assessed intraoperative findings, neurological and neurocognitive assessments, and ability to work following function-based maximal surgical resection attempts according to functional boundaries using intraoperative cortico-subcortical mapping under awake conditions in adult patients harboring a solitary brain metastasis within eloquent cortical and subcortical regions. In order to assess the efficacy and safety of awake surgery in the specific population of solitary brain metastasis patients, we performed a case-matched analysis with a control group of patients operated on with the same surgical technique for a high-grade diffuse glioma.

Material and methods

Study design and setting

This retrospective, observational study was conducted at a tertiary referral neurosurgical center for brain tumors (January 2014–December 2019). This study received approval (IRB#1: 2020/10) from the institutional review board (IRB00011687).

Awake metastasis group selection

Inclusion criteria were as follows: (1) ≥18 years, (2) solitary brain metastasis of non-neurogenic origin, (3) supratentorial tumor location within eloquent areas as previously defined [22], and (4) function-based resection with intraoperative cortico-subcortical mapping under awake conditions.

Four hundred twenty-three brain metastases in adult patients were operated on over the study period, 98 being located within eloquent areas. From the 98 metastases located within eloquent areas and surgically treated, 31 were excluded due to multiples brain metastases. From the 67 solitary metastases located within eloquent areas and surgically treated, 47 were operated on using asleep surgery without any functional mapping due to neurosurgeon's preference in 39 cases and due to contraindication to awake surgery in eight cases. We finally included 20 solitary metastases located within eloquent areas and operated on using intraoperative cortico-subcortical mapping under awake conditions (20.4% of eloquent brain metastases, 4.7% of the whole series).

Awake control group selection

In order to assess the safety of awake surgery in the specific condition of solitary brain metastasis patients, we performed a case-matched analysis with a control group of patients harboring a different disease, i.e., a high-grade glioma, and having operated on with the same surgical technique. All patients who underwent function-based resection for a high-grade glioma using the same surgical technique and during the same time period were screened. Each patient in the awake metastasis group was individually matched with a control patient according to the following criteria, listed in order of importance: (1) sex, (2) tumor location (same lobe, same side), (3) preoperative volume (within 25 cm^3), (4) preoperative Karnofsky Performance Status (KPS) score (within 10 points), (5) age (within 5 years), and (6) the same level of education (estimated using the Barbizet and Duizabo scale [2]). If no control matched in all five criteria, then sex, degree of education within one level, preoperative tumor volume of up to 50 cm^3, preoperative KPS score of up to 20 points, or a difference in age of > 5 years was accepted, in that order of preference. Table 1 shows the characteristics of each matched pair.

Variables and data sources

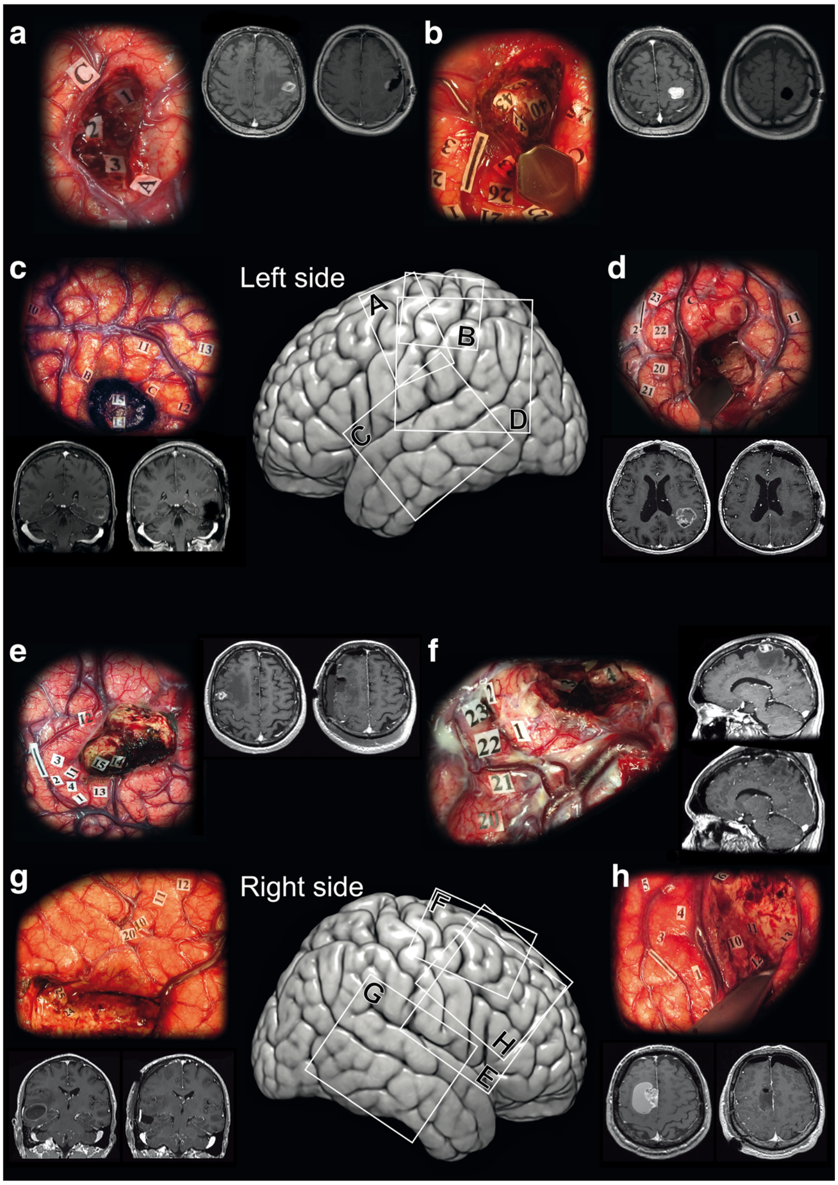
Patient-, surgery-, and tumor-related characteristics included the following: sex, age, previous oncological treatment, clinical sign(s) (increased intracranial pressure, focal neurological deficit, neurocognitive deficit, epileptic seizure), preoperative seizure control, KPS score, tumor location, tumor volume, duration of surgery, intraoperative seizure, current intensity for intraoperative mapping, extent of resection, histomolecular diagnosis, early postoperative seizure, early postoperative neurological status, early postoperative KPS score, duration of hospital stay, postoperative complications, mode of discharge, three-month seizure control, three-month neurological outcomes, and three-month KPS score.

The tumor volume (cm^3) was calculated using manual segmentation of abnormal signal on post-contrast T1-weighted

Table 3 Intraoperative characteristics

Parameters	Metastasis group			Control group		*p* value
	n		%	*n*	%	
Intraoperative characteristics						
Overall duration of the surgery (min)	Mean ± SD (range)	181.2 ± 34.7		237.6 ± 38.2		**<0.001**
Duration of the awake phase (min)	Mean ± SD (range)	63.2 ± 23.3		96.4 ± 18.2		**<0.001**
Current intensity for functional mapping (mA)	Mean ± SD (range)	3.6 ± 0.9		3.5 ± 1.0		0.766
	3 mA and <	9	45	9	45	1.0
	> 3 mA	10	55	10	55	
Awake procedure abortion	No	20	100	20	100	1.0
	Yes	0	0	0	0	
Time to emergence from anesthesia (min)	Mean ± SD (range)	14.7 ± 8.3		16.0 ± 8.0		0.463
	30 min and <	19	95	17	85	0.292
	> 30 min	1	5	3	15	
Postural pain	No	18	90	18	90	1.0
	Yes	2	10	2	10	
Intraoperative seizure	No	20	100	19	95	0.311
	Yes	0	0	1	5	

SD standard deviation



sequence by three blinded investigators (JBP, AM, and JP). The extent of resection was quantified on early postoperative MRI (within 48 hours) by manual segmentation of volume of residual tumor and of surgical cavity on post-contrast volumetric T1-weighted sequence by the same three blinded investigators. A supramarginal resection was defined as the complete removal of abnormal signal on post-contrast T1-weighted sequence plus the volume of the postoperative cavity being larger than the preoperative tumor volume as previously defined [19].

Language and neurocognitive functions were tested by a senior speech therapist before and after resection. The tests used are summarized in Supplementary Table 1. For each neurocognitive test, raw scores were converted to standardized scores using normative data that adjust for age, education, sex, ethnicity, and handedness, as appropriate. Before surgery, neurocognitive impairment on each test was defined as a standardized score ≥1.5 standard deviations below the normative mean. Postoperatively, declines or improvements in neurocognitive test performance were defined by using the Reliable Change Index. All Reliable Change Index thresholds were rounded to the nearest whole number. Changes that did not meet the Reliable Change Index criteria for decline or improvement were classified as stable.

Surgical procedure

Intraoperative functional mapping was performed using our in-house “asleep-awake-asleep” protocol [17, 28]. Functional mapping was conducted by direct electrical stimulation using a bipolar electrode (5-mm space between tips, biphasic current, pulse frequency of 60 Hz; pulse phase duration of 1 ms; Osiris NeuroStimulator, Inomed). Non-eloquent areas were identified to perform the corticectomy directed toward the metastasis, with

◀ **Fig. 1** Illustrative cases of brain metastasis maximal safe functional-based resection using direct cortico-subcortical electric stimulation under awake conditions to define functional boundaries. Intraoperative photographs showing the surgical field with the functional boundaries of the resection marked intraoperatively by numbered tags in the depth of the cavity and corresponding preoperative and postoperative magnetic resonance examinations. **a** Left fronto-central lung metastasis previously treated by stereotactic radiotherapy seven years ago discovered in a 74-year-old right-handed man presenting with epileptic seizures and right facial paresis (patient n°11). A partial resection was performed (numbered tags: involuntary movement of the face and mouth in 1, 2, and 3 identifying the primary motor subcortical pathways) and demonstrated a radionecrosis. **b** Left parietal non-seminomatous germ cell testis tumor metastasis in a 43-year-old right-handed man presenting with epileptic seizures and right upper limb paresthesia (patient n°20). A total resection was performed (numbered tags: involuntary movement of the thumb in 1, involuntary movement of the wrist in 2, and involuntary movement of the elbow in 3 identifying the primary motor cortical pathways; paresthesia of the fingers in 21, 22, 23, and 26, paresthesia of the chest in 25, paresthesia of the thumb in 41, and paresthesia of the lower limb 40, 42, 43 identifying sensory cortico-subcortical pathways). **c** Left temporal gastrointestinal metastasis in a 52-year-old right-handed man found on MRI check-up while asymptomatic (patient n°17). A supramarginal resection was performed (numbered tags: phonemic paraphasia in 11, latency and semantic paraphasia in 12, semantic paraphasia in 13, and latency in 14 and 15 identifying language cortico-subcortical pathways). **d** Left parietal renal cell carcinoma metastasis in a 78-year-old right-handed man found on MRI check-up while asymptomatic (patient n°12). A supramarginal resection was performed (numbered tags: involuntary movement of the mouth and tongue in 1, and involuntary movement of the hand in 2 identifying the primary motor cortical pathways; paresthesia of the mouth and tongue in 20 and 21, and paresthesia of the face in 22 and 23 identifying the sensory cortical pathways; semantic paraphasia in 11 and phonemic paraphasia in 12 identifying language cortico-subcortical pathways). **e** Right fronto-central lung metastasis previously treated by stereotactic radiotherapy nine months ago discovered in a 50-year-old right-handed man found on MRI check-up while asymptomatic (patient n°13). A total resection was performed (numbered tags: vocalization in 1 and speech arrest in 4 identifying language cortical pathways; involuntary movement of the tongue in 2 and 3 identifying the primary motor cortical pathways; arrest of voluntary movements of the upper limb in 11, 12, 13, 14, and 15 identifying cortico-subcortical negative motor networks) and demonstrated a radionecrosis. **f** Right fronto-central lung metastasis discovered in a 64-year-old right-handed man presenting with right lower limb paresis (patient n°18). A supramarginal resection was performed (numbered tags: involuntary movement of the chest in 1, involuntary movement of the hip in 2 and 3, and involuntary movement of the of the foot in 4 identifying the primary motor cortico-subcortical pathways; 20 paresthesia of the wrist in 20, paresthesia of the shoulder in 21, paresthesia of the trunk in 22, and paresthesia of the hip in 23 identifying sensory cortico-subcortical pathways). **g** Right tempo-parietal lung metastasis previously treated by whole brain radiation therapy six months ago discovered in a 48-year-old left-handed man presenting with language disturbances (patient n°10). A total resection was performed (numbered tags: hypophonia in 10, latency in 11, dysarthria in 12, and phonemic paraphasia in 20 identifying language cortical pathways; blurring of the visual field in 24 and 25 identifying the visual pathways). **h** Right fronto-central melanoma metastasis discovered in a 50-year-old right-handed man presenting with left lower limb paresis (patient n°5). A supramarginal resection was performed (numbered tags: involuntary movement of the wrist in 1 and 2, involuntary movement of the elbow in 3 and 4, involuntary movement of the shoulder in 5, and involuntary movement of the lower limb in 6 identifying the primary motor cortico-subcortical pathways; arrest of voluntary movements of the upper limb in 10, 11, 12, and 13, identifying subcortical negative motor networks; saccadic eye deviation in 13 identifying subcortical pathways underpinning eye movements).

assistance from intraoperative MRI-based neuronavigation and ultrasonography. To control for neurological and cognitive function, intraoperative tasks were performed, including motor network, somatosensory network, language, calculation, memory or even visuospatial processing, semantic cognition (*pyramid and palm tree* test), and social cognition (modified version of the *reading the mind in the eyes* test), depending on glioma location and according to practical guidelines [8, 16, 17]. The patient was monitored by continuous execution of the required tasks throughout the metastasis resection and the types of disturbances were classified by a senior speech therapist. The metastasis was resected *en bloc*, whenever possible, by alternating dissection and stimulation for subcortical functional mapping at the tumor wall and at the periphery of the metastasis. In all patients, repeated ultrasonography was performed throughout the resection to control for anatomical landmarks. Each subcortical anatomical site inducing the same and reproducible functional impairment on three trials was considered as “eloquent” and was marked with a sterile numbered tag, were located and registered using MRI-based neuronavigation system, and intraoperative photographs were performed at the end of the resection. Resections were stopped when eloquent subcortical structures defining the deep functional boundaries were identified intraoperatively using dedicated intraoperative tasks within the surgical cavity with no security margin of brain tissue left around the functional connectivity or until the patient felt too tired to work efficiently.

Statistical analyses

Descriptive statistics were given as the mean ± standard deviation for continuous variables and as a percentage for categorical variables. Univariate analyses were carried out using the chi-square 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. A p value of less than 0.05 was considered significant. Analyses were performed using JMP 14.1.0 (SAS Institute Inc, Cary, North Carolina, USA).

Results

Patient characteristics

Twenty patients (60.5% men, mean age 55.6±11.4-year-old) were included. Clinical and imaging characteristics are detailed in Table 2.

There were no significant differences between the metastasis and control groups in sex ratio, age, education, increased intracranial pressure, focal neurological deficit, seizure control, KPS score, tumor location, and tumor volume. There were fewer seizures (50% vs. 85%, p=0.016) and more previous oncological treatments before surgery (70% vs. 15%, p<0.001) in the metastasis group than in the control group.

Awake surgery

Intraoperative characteristics are detailed in Table 3. All patients were cooperative; there were no obstacles that precluded a function-based resection from being performed (no intraoperative seizures, postural pain in 10%). Intraoperatively, positive functional mapping was achieved in all patients at both cortical and subcortical levels (mean stimulation current intensity 3.6±0.9 mA). The overall duration of the surgery (181.2±34.7 *versus* 237.6 ± 38.2 min, p<0.001) and the duration of the awake phase (63.2±23.3 *versus* 96.4±18.2 min, p<0.001) were significantly shorter in the metastasis group than in the control group.

A total resection was performed in 18 cases (90%, including 10 cases (50%) of supramarginal resection), and a partial resection was performed in the remaining two cases (10%, two radionecrosis). In all cases, resection was pursued until eloquent subcortical pathways were identified, including in the two cases with partial resection, as illustrated in Fig. 1.

Postoperative outcomes

In the early postoperative period, clinical worsening occurred in five cases (25%), seizures occurred in two cases (10%), KPS score decreased at 76.5±10.9, surgical site infection occurred in two cases (10%), and medical complications occurred in three cases (15%, two urinary tract infections, one hemoptysis). Eighteen patients (90%) were discharged home. The length of hospital stay was similar in the metastasis and in the control groups (median 9 vs. 8 days, p=0.118) with a 240-day-long hospital stay for a postoperative infection in one metastatic patient. All patients underwent personalized rehabilitation. The 15 patients with a histologically confirmed metastasis received postoperative focal radiotherapy whereas the five patients with radionecrosis had no further focal treatment.

The evolution of the clinical and neurocognitive statuses before and after awake surgery are detailed in Table 4. At three postoperative months, two patients had died from the systemic evolution of their neoplasm. As compared to the preoperative evaluation, none of the patients had worsening of their neurological condition or uncontrolled seizures, three patients had an improvement in their seizure control, and seven patients had a KPS score increase ≥10 points.

A postoperative neurocognitive evaluation has been performed in nine cases (45%) at a mean 200±50 days (nine patients had a neoplasm evolution precluding the evaluation to be performed and two patients declined the evaluation). Two patients (22.2%) improved, five patients (55.6%) remained stable, and two patients (22.2%) worsened as compared to the preoperative neurocognitive evaluation.

Discussion

Key results

In this case-matched analysis of 20 adult patients harboring a brain metastasis within eloquent regions and undergoing a function-based resection under awake conditions, we show that (1) there were no obstacles precluding function-based resection from being performed in all patients; (2) there were no major differences in the feasibility of the awake procedure between metastasis patients and high-grade gliomas patients; 3) the function-based resection was total in 18 cases (90%, including 10 cases of supramarginal resection), and partial in two cases (10%); (4) at three months postoperative, none of the patients had worsening of their neurological condition or uncontrolled seizures, seven patients had a KPS score increase ≥10 points compared to the preoperative evaluation; and (5) on postoperative neurocognitive evaluation, available in nine cases, 22.2% of patients improved, 55.6% of patients remained stable, and 22.2% of patients worsened compared to the preoperative neurocognitive evaluation.

Interpretation

We provide a detailed case-matched analysis of intraoperative findings between function-based resection under awake conditions of brain metastases and the well-established technique applied for high-grade gliomas. Despite the presence of previous oncological treatments before awake surgery in 75% of patients from the metastasis group, we did not find an increase in technical difficulties and complications compared to the control group. Particularly, a function-based resection according to functional boundaries was achieved in all patients. We report similar complication rates compared to the previous published series [7, 21]. Kamp et al. studied the safety of awake resection for metastases in eloquent brain areas: they reported a series of supramarginal resections with no difference in median National Institute of Health Stroke Scale between the pre- and postoperative evaluations and no new permanent neurological deficits after surgery [9]. The present data suggest that function-based resection using awake brain mapping is a safe and effective tool to remove brain metastases within eloquent areas [4, 9, 21]. The expertise accumulated from glioma resection could be easily transferred in selected metastasis patients [17].

Table 4 Clinical, epileptic seizure, and cognitive status before and after awake surgery

Pt.	Tumor location	Handedness	KPS status			Epileptic seizure status			Preoperative cognitive evaluation				Evolution of the postoperative cognitive evaluation				
			Preop	Postop	Post/pre	Preop	Postop	Post/pre	Language function	Executive function	Memory function	Attention function	Date	Language function	Executive function	Memory function	Attention function
1	L, middle frontal gyrus	R	90	100	↑	No seizure	No seizure	=	Normal	Normal	Normal	Normal	Declined				
2	L, inferior frontal gyrus	R	80	90	↑	Controlled	Controlled	=	Normal	Altered	Altered	Normal	+120 D	=	↑	↑	=
3	L, middle and inferior temporal gyri	R	70	Death		Controlled	Death		Altered	Altered	Altered	Normal	Death				
4	L, inferior frontal gyrus	R	80	80	=	No seizure	No seizure	=	Altered	Altered	N/A	N/A	Death				
5	R, superior frontal gyrus	R	80	Death		No seizure	Death		Normal	Altered	Altered	Altered	Death				
6	R, middle frontal gyrus	L	90	90	=	No seizure	No seizure	=	Normal	Normal	Normal	Normal	+ 300 D	=	=	=	=
7	L, post-central gyrus	R	80	100	↑	Controlled	Controlled	=	Altered	Altered	Altered	Altered	+180 D	=	=	=	=
8	R, post-central gyrus	R	70	60	↓	Controlled	Controlled	=	Normal	Altered	Altered	Normal	Death				
9	L, superior and middle temporal gyri, supra-marginal gyrus	R	70	50	↓	Controlled	Controlled	=	Declined				Death				
10	R, supra-marginal gyrus	R	70	70	=	No seizure	No seizure	=	Normal	Altered	Normal	Normal	Death				
11	L, pre-central gyrus	R	60	60	=	Controlled	Controlled	=	Emergency				Death				
12	L, post-central gyrus	R	90	90	=	No seizure	No seizure	=	Normal	Altered	Normal	Altered	+210 D	=	=	↓	=
13	R, pre-central gyrus	R	90	90	=	Uncontrolled	Controlled	↑	Normal	Altered	Normal	Altered	+240 D	=	↑	=	↑
14	L, superior temporal gyrus	R	100	80	↓	No seizure	No seizure	=	Altered	Normal	Normal	Altered	Declined				
15	R, middle frontal gyrus	R	90	90	=	No seizure	No seizure	=	Normal	Altered	Normal	Normal	+210 D	↓	=	↓	↓
16	L, sup. middle and inferior temporal gyri	R	70	80	↑	Uncontrolled	Controlled	↑	Altered	Normal	Altered	Normal	+180 D	=	=	=	=
17	L, middle temporal gyrus	R	90	100	↑	Controlled	Controlled	=	Normal	Normal	Normal	Normal	Declined				
18	R, pre-central gyrus	R	90	100	↑	No seizure	No seizure	=	Normal	Normal	Normal	Normal	+180 D	=	=	=	=
19		R	90	80	↓	No seizure	No seizure	=	Altered	Normal	Altered	Normal	+180 D	=	=	↑	=

Table 4 (continued)

Pt.	Tumor location	Handedness	KPS status			Epileptic seizure status			Preoperative cognitive evaluation				Evolution of the postoperative cognitive evaluation				
			Preop	Postop	Post/pre	Preop	Postop	Post/pre	Language function	Executive function	Memory function	Attention function	Date	Language function	Executive function	Memory function	Attention function
	L, hippocampal formation																
20	L, post-central gyrus	R	80	100	↑	Uncontrolled	Controlled	↑	Normal	Normal	Altered	Normal	Death				

KPS Karnofsky Performance Status, ↑ improved, = stable, ↓ decreased, *D* day, *L* left, *R* right

We reported 25% of clinical worsening in the early postoperative period, no new permanent neurological deficits, and no uncontrolled seizures at three months postoperative as well as stable KPS scores despite postoperative adjuvant oncological treatments. A systematic review by Chua et al., analyzing 104 patients from seven studies undergoing awake craniotomy for a metastasis, reported 27% of persistent or worsened neurological deficits in the early postoperative period and reported 1% of permanent neurological deficits at follow-up [4]. Sanmillan et al., in a series of 31 patients operated on for a brain metastasis within eloquent areas using awake functional mapping or asleep monitoring (evoked potentials), reported that patients who had a worsened clinical outcome postoperatively had a shorter overall survival, the postoperative KPS score being a strong predictor [21]. The completion of postoperative cognitive evaluations was limited by the tumor evolution; we observed, in the nine available cases, stable and improved cognitive functions in 56%, and 22% of cases, respectively, compared to the preoperative neurocognitive evaluation despite the application of postoperative oncological treatments. Other studies have demonstrated a similar relationship between functional status and survival [1, 13, 23, 24]. Similarly, the present study suggests that intraoperative functional mapping under awake conditions allows for both a safe and large resection of metastases in eloquent brain areas, which may be associated with survival benefits.

The extent of resection is a crucial component of achieving local control [3, 18] since most brain metastases display an irregular tumor-brain interface at a microscopic scale [15]. Supramarginal resection aims to improve local control [27] by removing the peripheral brain parenchyma possibly containing scarce tumor cells. Here, the 50% rate of supramaximal resection supports awake resection as a useful technical adjunct to improve local control of brain metastases within eloquent areas. Of note, a function-based partial resection has been performed in two cases where subcortical functional mapping identified eloquent pathways embedded within a radionecrosis. This is of particular interest in situations of metastases previously treated by radiotherapy, where radiation-induced changes can be nested within eloquent areas, to minimize surgical risks.

Generalizability

To control for selection biases in the assessment of the safety of awake surgery in the specific condition of solitary brain metastasis patients, we performed a case-matched analysis with a control group of patients operated on using the same surgical technique for a high-grade diffuse glioma. Previous studies limited their analysis to the gross total resection or reported a subjective intraoperative evaluation of the supramarginal resection [4, 10, 27]. The present study controlled for this bias by quantifying the extent of resection on early postoperative MRI.

Limitations

These findings should be interpreted with caution, given the exploratory and retrospective design of the study, the small sample size including patients with different primary neoplasms, and data missing for 55% of postoperative cognitive evaluations. Inclusion biases may limit the generalizability to the overall population of adult patients with metastases within eloquent brain areas. A prospective data collection would be necessary to better assess neurocognitive outcomes.

Conclusions

Function-based resection under awake conditions preserving the brain connectivity is feasible and safe in the specific population of solitary brain metastasis patients and allows for high rates of total resection for metastases within eloquent brain areas while preserving the overall and neurological condition of the patients. Awake craniotomy should be considered as a possible surgical technique to optimize outcomes in brain metastases in eloquent areas.

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Data availability Not applicable.

Code availability Not applicable.

Declarations

Ethics approval This study received approval (IRB#1: 2020/10) from the institutional review board (IRB00011687).

Consent to participate Due to the retrospective nature of the study no consent was obtained.

Consent for publication Due to the retrospective nature of the study no consent was obtained.

Conflict of interest The authors have no conflict of interest to disclose.

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