JNS
CLINICAL ARTICLE
J Neurosurg 126:698–707, 2017

Functional approach using intraoperative brain mapping and neurophysiological monitoring for the surgical treatment of brain metastases in the central region

Jose L. Sanmillan, MD,[1] Alejandro Fernández-Coello, MD,[1] Isabel Fernández-Conejero, MD,[2] Gerard Plans, MD,[1] and Andreu Gabarrós, MD, PhD[1]

Departments of [1]Neurosurgery and [2]Neurophysiology, Hospital Universitari de Bellvitge, Barcelona, Spain

OBJECTIVE Brain metastases are the most frequent intracranial malignant tumor in adults. Surgical intervention for metastases in eloquent areas remains controversial and challenging. Even when metastases are not infiltrating intraparenchymal tumors, eloquent areas can be affected. Therefore, this study aimed to describe the role of a functional guided approach for the resection of brain metastases in the central region.

METHODS Thirty-three patients (19 men and 14 women) with perirolandic metastases who were treated at the authors' institution were reviewed. All participants underwent resection using a functional guided approach, which consisted of using intraoperative brain mapping and/or neurophysiological monitoring to aid in the resection, depending on the functionality of the brain parenchyma surrounding each metastasis. Motor and sensory functions were monitored in all patients, and supplementary motor and language area functions were assessed in 5 and 4 patients, respectively. Clinical data were analyzed at presentation, discharge, and the 6-month follow-up.

RESULTS The most frequent presenting symptom was seizure, followed by paresis. Gross-total removal of the metastasis was achieved in 31 patients (93.9%). There were 6 deaths during the follow-up period. After the removal of the metastasis, 6 patients (18.2%) presented with transient neurological worsening, of whom 4 had worsening of motor function impairment and 2 had acquired new sensory disturbances. Total recovery was achieved before the 3rd month of follow-up in all cases. Excluding those patients who died due to the progression of systemic illness, 88.9% of patients had a Karnofsky Performance Scale score greater than 80% at the 6-month follow-up. The mean survival time was 24.4 months after surgery.

CONCLUSIONS The implementation of intraoperative electrical brain stimulation techniques in the resection of central region metastases may improve surgical planning and resection and may spare eloquent areas. This approach also facilitates maximal resection in these and other critical functional areas, thereby helping to avoid new postoperative neurological deficits. Avoiding permanent neurological deficits is critical for a good quality of life, especially in patients with a life expectancy of over a year.

https://thejns.org/doi/abs/10.3171/2016.2.JNS152855

KEY WORDS brain mapping; neurophysiological monitoring; brain metastases; eloquent area surgery; oncology

Brain metastases are the most frequent intracranial neoplasms in adults and are diagnosed in up to 40% of patients with a systemic tumor.[15] The rising incidence of brain metastases is due to better control of systemic disease and the development of new and powerful diagnostic tools that allow early and accurate diagnosis. However, because brain metastases carry a poor prognosis, prompt multidisciplinary treatment is mandatory.[49]

Resection followed by radiotherapy is currently the most common treatment for solitary brain metastases and can provide excellent local tumor control[15,18,30]; however, as we will discuss further, when a metastasis involves the eloquent cortex, stereotactic radiosurgery (SRS) or whole-brain radiation therapy (WBRT) is preferred in some centers. It has been argued that treatment strategies should be individualized to the patient,[1,49] not least because besides surgery other treatment options exist, including SRS, chemotherapy, and effective supportive care. Optimal resec-

ABBREVIATIONS CST = corticospinal tract; DCS = direct cortical stimulation; DTI = diffusor tensor imaging; EBS = electrical brain stimulation; KPS = Karnofsky Performance Scale; MEP = motor evoked potential; SMA = supplementary motor area; SRS = stereotactic radiosurgery; TES = transcranial electrical stimulation; WBRT = whole-brain radiation therapy.

SUBMITTED December 6, 2015. **ACCEPTED** February 5, 2016.
INCLUDE WHEN CITING Published online April 29, 2016; DOI: 10.3171/2016.2.JNS152855.

tion can reduce mass effect, improve neurological status, and improve survival while retaining reasonably low morbidity rates.[26,34] Despite this, the surgical treatment of brain metastases located in eloquent areas remains controversial because surgery is challenging and there is a risk of new permanent neurological deficits in the postoperative period.[9,25] Consequently, brain metastases located in these areas have classically been approached with less-invasive treatment options.[9]

Brain metastases tend to be located in the cortical-subcortical junction and are surrounded by nontumoral white matter. The brain tissue around brain metastases, such as that located in an eloquent area, can be essential for neurological function and is often disrupted even during the resection of extraaxial tumors. We argue that neurological outcome could be improved after surgical treatment of brain metastases in eloquent areas by using a planned intraoperative functional approach for those tumors. Indeed, intraoperative brain mapping techniques have been demonstrated to be useful for the resection of intrinsic lesions. In a recent meta-analysis, the use of intraoperative stimulation brain mapping was associated with fewer late severe neurological deficits and more extensive resection in patients with high- and low-grade gliomas.[8] Furthermore, intraoperative brain mapping has been described as useful during the surgical resection of extraparenchymal lesions, such as arteriovenous malformations.[14]

Different neurophysiological techniques have been described to evaluate eloquent brain function intraoperatively. Since the first electrical brain stimulation (EBS) cases were reported by Penfield and Boldrey,[31] intraoperative EBS has evolved to become the gold standard for localizing and assessing function during surgery. A functional approach that uses intraoperative mapping techniques combined with neurophysiological monitoring allows the delimitation of cortical eloquent areas, as well as subcortical functional boundaries, and can help preserve both during tumor resection. However, although EBS techniques are recommended by some authors for the resection of metastases,[16,40] implementation is incompletely reported and its use remains poorly defined.

In the present article, we explain the surgical protocol for the functional approach that is applied at our institution, and we discuss the usefulness of functional assessment. We focus on our experiences with the resection of metastases in the eloquent brain areas of patients with single perirolandic metastases.

Methods

Patients

We retrospectively searched the tumor database of our institution for patients with centrally located, single parenchymal brain metastases who underwent resection with the assistance of intraoperative neurophysiological monitoring and/or brain mapping between 2003 and 2013. The search yielded 33 adults, each with a single brain metastasis that was located in the precentral gyrus, postcentral gyrus, or immediately adjacent to these locations. Patients were excluded if they underwent biopsy or had a metastasis smaller than 3 cm at its greatest diameter. All included patients had controlled extracranial disease, a life expectancy longer than 6 months, and a preoperative Karnofsky Performance Scale (KPS) score greater than 70%.

Table 1 summarizes the patient characteristics. There were 19 men (57.6%) and 14 women (42.4%) with a mean age of 56.4 years (range 37–78 years). The mean preoperative KPS score was 83.0% ± 9.83%. Metastases originated from lung cancer (n = 17), breast cancer (n = 7), kidney cancer (n = 5), rectal cancer (n = 2), malignant melanoma (n = 1), and parotid gland cancer (n = 1). The initial clinical presentation was seizure (n = 13; 39.4%) or hemiparesis (n = 11; 33.3%) in most cases. Other presenting symptoms were headache (n = 3), sensory disturbances (n = 2), mild dysphasia (n = 1), and behavioral disturbances (n = 1). Two patients were asymptomatic at diagnosis.

Preoperative assessment was MRI with spectroscopy and diffusor tensor imaging (DTI) sequences. For those patients in whom, due to the size of the metastasis, classic anatomical language functional areas (e.g., Broca's and/or Wernicke's areas) were affected and in whom language was slightly impaired during clinical evaluation (e.g., impaired verbal fluency, impaired sentence repetition, or impaired object naming), we performed both preoperative functional MRI and neuropsychological evaluation. We also performed these 2 preoperative tests in those patients in whom the metastasis affected the posterior area of the superior frontal gyrus of the dominant hemisphere. Number counting, noun generation, and picture-naming tasks were performed by all patients during functional MRI and neuropsychological evaluation, and these were reproduced during surgery in awake mapping cases. All patients underwent postoperative gadolinium-enhanced MRI. Short-term follow-up was performed at the moment of hospital discharge. Cases were evaluated after surgery in a multidisciplinary team meeting, and periodic MR images were obtained during follow-up.

Surgery

According to our institutional protocol based on European guidelines,[41] surgery followed by WBRT is recommended—and preferred to radiotherapy alone—for all patients who had a single, reachable brain metastasis greater than 3 cm at its greater diameter as well as good functional status and a controlled primary tumor, even if the patient was asymptomatic at the moment of diagnosis. The peculiarity of the patients included in our series is that they all had lesions located in a highly eloquent brain area. Therefore, instead of changing treatment to SRS because of the eloquence of the brain area, we offered all patients surgery with the intent to remove all of the lesion using a functional guided approach with intraoperative neurophysiological monitoring and/or brain mapping in order to attend to the affected structures in each patient and minimize the risk of permanent postoperative neurological deficit (Fig. 1).

Twenty-four patients (72.7%) with lesions surrounding the central sulcus underwent surgery while asleep, and 9 (27.3%) patients with lesions extending to and affecting dominant perisylvian areas (4 patients) or dominant supplementary motor areas (SMAs) (5 patients) underwent surgery under awake conditions. Awake surgery allowed intraoperative language assessment of the patients with tumors located in perisylvian areas. We also performed surgery under awake conditions to identify complex motor

TABLE 1. Demographic and clinical preoperative data

Characteristic	Value*
Sex	
Male	19 (57.6)
Female	14 (42.4)
Age, yrs	
Median	56.4
Range	37–78
Primary tumor location	
Lung	17 (51.5)
Breast	7 (21.2)
Kidney	5 (15.2)
Rectum	2 (6.1)
Melanoma	1 (3.0)
Parotid gland	1 (3.0)
Presenting symptoms	
Seizures	13 (39.4)
Hemiparesis	11 (33.3)
Headache	3 (9.1)
Sensory disturbances	2 (6.1)
Dysphasia	1 (3.0)
Behavioral disturbances	1 (3.0)
Asymptomatic	2 (6.1)

* Data are presented as number of patients (%) unless otherwise stated.

movements and specific language function in the dominant SMA because damage to the SMA during the tumor approach or resection has been shown to cause permanent neurological deficits, especially when involving the SMA in the dominant hemisphere.[13] The surgical protocol used in our department is briefly outlined below.

General Surgical Considerations

Total intravenous anesthesia was performed using propofol (5–10 mg/kg/hour) and remifentanil (0.01–0.03 μg/kg/minute). The use of muscle relaxants was avoided. Antibiotic prophylaxis was cefuroxime (1.5 g) administered 30 minutes before skin incision. Once the patient was anesthetized, the head was fixed to the operating table with a Mayfield 3-pin fixation device. The skin wound was injected with a local anesthetic solution composed of 0.5% bupivacaine and 2% lidocaine. Craniotomy was tailored with the help of a frameless neuronavigation system (Brainlab). Anticonvulsant therapy was administered preoperatively, intraoperatively, and postoperatively to all patients suffering seizures at presentation. Those patients who were eligible to undergo awake surgery were treated at least 1 week before surgery with anticonvulsant therapy. If stimulation-evoked seizures occurred during the procedure, iced Ringer's lactate was applied directly onto the brain cortex[13,23,37] and anticonvulsant therapy was initiated immediately and maintained during at least the postoperative period.

Asleep Surgery

Motor function in asleep patients was evaluated by motor evoked potentials (MEPs). In patients under general anesthesia, MEPs were obtained after transcranial electrical stimulation (TES) and/or direct cortical stimulation (DCS) with a short train of stimuli.[43] For TES, scalp spiral "corkscrew" needles were placed on the measured sites over the motor cortex (International 10–20 electroencephalography system).[42] For DCS, a subdural grid of 8 contacts was placed over the sensorimotor cortex.

The stimulation parameters consisted of a short train of stimuli (3–5 pulses), each 500 μsec in duration, with a 4-msec interstimulus interval and intensities of up to 150 mA for TES and 20 mA for DCS. MEPs were recorded from bilateral muscles, including the extensor digitorum communis, abductor pollicis brevis, tibialis anterior, and abductor hallucis. This allowed monitoring of the functional integrity of the corticospinal tract (CST) and specific muscles based on the tumor location and its relation to the surrounding eloquent cortex. A pair of subdermal needles was inserted into each muscle to record the MEPs.[22] In supratentorial surgeries, MEPs elicited by DCS were preferable because they are more focal than TES and do not risk stimulating deeper than the cortical-subcortical level. Once the dura mater was opened, a strip electrode with 8 contacts (each 4 mm in diameter and with interelectrode distance of 10 mm) was placed over the sensorimotor cortex. Functional localization of the central sulcus was done by recording the N20–P20 phase reversal somatosensory evoked potentials with a subdural grid.[5,35] The electrode selected from the grid to elicit MEPs was the one that produced the highest amplitude response with the lowest intensity of stimulation. MEPs were continuously recorded through the surgical procedure.

A neuronavigation system was used to locate the lesion. The same stimulation parameters were used for brain mapping (electrical identification of motor cortical areas or subcortical motor tracts). A hand-held monopolar electrode was used, with anodal and cathodal stimulation used for cortical and subcortical mapping, respectively. Cortical mapping was used to identify functional and nonfunctional cortical areas around the lesion and to perform safe corticotomy without damaging the motor cortex. When a functional area was stimulated with the electrode, the neurophysiologist recorded the MEPs and advised the surgeon about the functionality of the area, the stimulated muscle or muscles, and the intensity of the stimulus required to elicit the response.

Corticotomy was performed in a noneloquent cortical area and directed toward the lesion. Total en bloc microsurgical resection was performed whenever possible. During the procedure, if proximity to a motor pathway was suspected, subcortical monopolar stimulation was performed to provide feedback about proximity to the CST. This was performed starting at 15 mA, which has been shown to be a safe threshold.[28] If MEPs were registered, decreasing intensity stimulations were done at the same subcortical area until MEPs were no longer registered. When a positive MEP response was found at 5 mA, the critical proximity to the functional pathway was assumed and extreme caution was taken during resection in this area to avoid damaging the surrounding brain parenchyma. Once total macroscopic resection was completed, we used transcranial, cortical, and subcortical

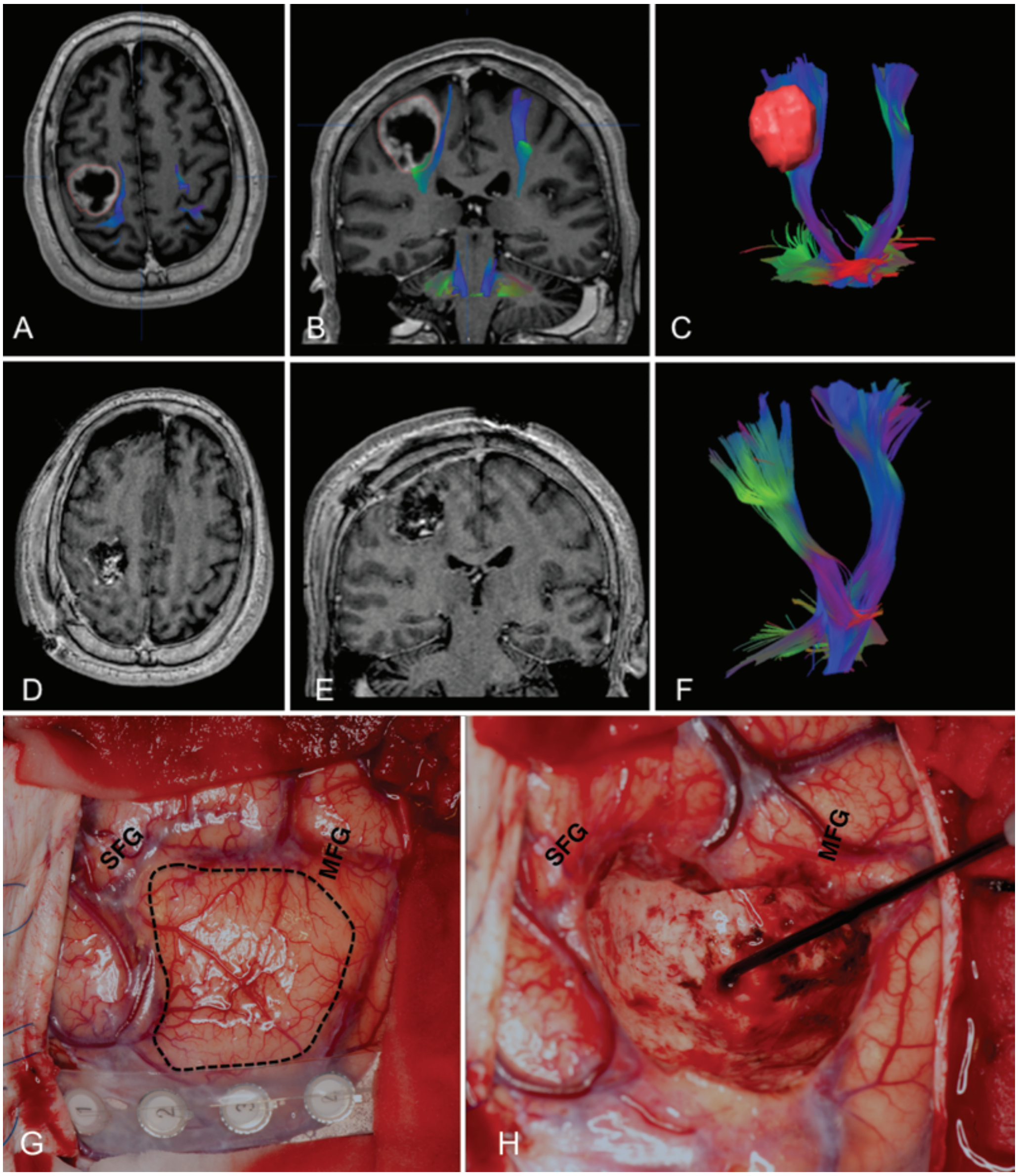

FIG. 1. A: Axial T1-weighted MR image obtained after gadolinium administration, demonstrating a subcortical lesion in the right frontal lobe with peripheral contrast enhancement allocated in the middle frontal gyrus immediately anterior to the right motor cortex. **B:** The proximity and relationship is noted between the deep surface of the lesion and the descending fibers of the right motor pathway when observed in the coronal plane. **C:** DTI sequence with 3D reconstruction of the motor pathways and volumetric reconstruction of the lesion. Note the displacement and distortion of the right motor tract caused by the tumor. **D and E:** Postoperative T1-weighted MR images after gadolinium administration in the axial (D) and coronal (E) planes, showing the total resection of the lesion. **F:** Postoperative DTI sequence with 3D reconstruction of the motor pathways, showing the distortion of the right motor tract after the surgery. The patient presented with postoperative worsening of the preoperatively existing left-arm paresis without developing any new motor deficit. **G:** Intraoperative photograph showing the 8-contact electrode strip placed over the motor cortex. The electrode strip elicited a motor response in the proximal muscles of the left inferior limb when Electrodes 1 or 2 were stimulated and a motor response of the left hand when Electrode 3 was stimulated. The *dotted line* demarcates the area selected for corticotomy. The area was demarcated after the nonfunctionality of the area was checked with cortical motor mapping using a hand-held monopolar electrode. **H:** Intraoperative photograph obtained once the metastasis resection was finished. Subcortical mapping with a hand-held monopolar electrode is performed during resection and when resection is finished to assess the functionality and the distance of the corticospinal tract in the areas where close proximity to the corticospinal tract is suspected. MFG = middle frontal gyrus; SFG = superior frontal gyrus. Figure is available in color online only.

stimulation at the resection margins to check the anatomical-functional integrity of the motor function network[11] and predict the patient's postoperative clinical status and recovery (Fig. 1).

Awake Surgery

In cases where tumors affected dominant perisylvian structures or dominant-sided SMAs, we used an awake mapping procedure during resection to identify language and complex motor function sites. Just before opening the dura mater, we administered mannitol, discontinued sedatives, and woke the patient. After opening the dura mater, a bipolar electrode Ojemann cortical stimulator (Radionics, Inc.) with an interelectrode distance of 5 mm was used to stimulate the brain. The electrode was set to deliver a biphasic current with a 60-Hz pulse frequency and a 1-msec single-pulse phase duration. The duration of each stimulation was 3 seconds in all cases.

Brain mapping began with stimulation of the facial area of the motor cortex in order to set the stimulation parameters by eliciting speech arrest; testing started with an intensity of 1 mA and progressively increased by 0.5-mA increments until the desired response was evoked. The smallest intensity that provoked speech arrest while the patient performed a counting task was used during cortical mapping. The sensorimotor cortex was stimulated when the extension of the tumor also affected those functional areas. A numbered sterile plastic label was placed in locations where movement or sensory response was elicited. After sensorimotor stimulation, perisylvian structures or the dominant superior frontal gyrus was stimulated using the same intensity. Language function was tested while the patient performed the picture-naming task during brain stimulation.[13,23] To monitor SMA function, in cases in which this is required, the patient performed 2 complex motor tasks. The first task was the finger-to-thumb task, which was performed with both hands consecutively in a complex, self-paced sequence beginning with the little finger and followed by the middle finger, ring finger, and finally the index finger opposition. The second task was the bimanual hand coordination task, which consisted of flexion and extension of both hands with a phase shift of 180° between them.[13,23,39] The verb generation task was used to explore the language function of the SMA.[4,6,20] When a functional SMA area was stimulated, it elicited a response that consisted of a blockade in the execution of language or SMA-required tasks. For the language assessment, we considered semantic and phonemic paraphasia, speech arrest, anomia, perseverations, or articulatory disorders as positive mapping responses. At least 2 of 3 positive stimulations were required to consider an area as functional in all mapping modalities. When a site was considered functional, it was marked with a numbered plastic label.

Nonlabeled areas were selected to approach the lesion, which was assisted by demarcation by the neuronavigation system. During microsurgical resection, motor control of the subcortical function around the tumor was assessed by continuous movement requests, and subcortical language or SMA function was monitored by continuous execution of the specific tests mentioned above. Alteration of any function during resection of the tumor margins obligated the neurosurgeon to stop resection and confirm the findings by subcortical stimulation. When a subcortical pathway was identified, great care was taken during further dissection of the tumor wall at this site, with particular attention given to avoiding damage to the surrounding brain; however, we still aimed to achieve a total en bloc microsurgical resection whenever possible. Once the lesion was totally removed, the patient was anesthetized using a laryngeal mask and surgical closure was performed.

Statistical Analysis

Descriptive analysis of the clinical data was done at baseline, in the postoperative period, and during follow-up. We used paired t-tests to compare preoperative KPS scores with postoperative KPS scores and compare postoperative KPS scores with follow-up KPS scores (measured at 6 months). Spearman's correlation test was used to compare preoperative and postoperative KPS scores with the survival period. A significance level of 5% was accepted for the comparisons.

For comparison of outcomes, patients were stratified into 3 groups by postoperative KPS score, as follows: Group 1, KPS Score 0% to 40% and unable to care for self; Group 2, KPS Score 50% to 70%, unable to work, and varying amount of assistance needed; and Group 3, KPS Score 80% to 100% and able to carry out normal activity and work. Kaplan-Meier survival curve analyses were done to show differences in survival among the groups. We used IBM SPSS (version 21.0; IBM Corp.) to perform the statistical analyses.

Results

The use of a functional guided approach by means of brain stimulation was used to guide the corticotomy and the limits of the resection in all cases.

A postoperative gadolinium-enhanced, T1-weighted MRI scan revealed the total removal of the tumor in 31 patients (93.9%). In 2 patients, total resection was not achieved. Each patient had a metastasis of the motor area and demonstrated functional parenchyma attached to the tumor during intraoperative functional assessment. The neurophysiologist reported a significant decrease in MEPs during tumor capsule manipulation. Subcortical stimulation revealed a positive MEP response at 5 mA. These 2 patients presented with postoperative moderate-to-severe hemiparesis that resolved within 3 months. After WBRT, no relapse was found in these 2 patients. In total, 28 patients (84.8%) received WBRT after surgery. One patient did not receive WBRT due to early death, and 4 patients did not receive WBRT due to bad performance status prior to radiotherapy. These 4 patients did not receive WBRT due to bad clinical status secondary to systemic progression of their primary tumor. All 4 patients had a survival period less than 4 months. There were 3 patients with local relapse of the tumor (9.0%), and stereotactic fractionated radiotherapy was applied to all relapsed metastases.

Postoperatively, 27 patients (81.8%) showed improvement or no change in their initial symptoms. However, 6 patients (18.2%) showed a clinical worsening after surgery, 4 patients with preexisting weakness developed a worsening in their paresis, and 2 patients developed new sensory disturbances. All 6 new neurological deficits were transitory, with total recovery within 3 months in all cases (Table 2).

After 6 months of follow-up, 6 patients died. In 5 patients, death was due to systemic progression of the primary tumor. However, 1 patient died following accidental vascular damage during surgery, which led to venous infarction, edema, intracranial hypertension, and death on postoperative Day 3.

One intraoperative partial motor seizure occurred (3%)

TABLE 2. Patient clinical data

Patient No.	Brain Metastasis Location*	Greatest Diameter (mm)	Presentation Symptoms	Awake vs Asleep Mapping	Functions Assessed During Surgery	Intraoperative Seizures	Amount of Resection Achieved	Postoperative Functional Impairment
1	SMA	33	Seizures	Awake	Motor, sensory & SMA	NA	Total	NA
2	SMA	30	Headache	Awake	Motor, sensory & SMA	NA	Total	NA
3	Motor cortex	30	Headache	Asleep	Motor & sensory	NA	Total	NA
4	Sensory cortex	30	Asymptomatic	Asleep	Motor & sensory	NA	Total	NA
5	Sensory cortex	64	Seizures	Asleep	Motor & sensory	NA	Total	NA
6	Sensory cortex	32	Seizures	Asleep	Motor & sensory	NA	Total	NA
7	Sensory cortex	33	Sensory disturbances	Asleep	Motor & sensory	NA	Total	NA
8	Motor cortex	35	Dysphasia	Asleep	Motor & sensory	NA	Total	NA
9	Sensory cortex	39	Seizures	Asleep	Motor & sensory	NA	Total	NA
10	Sensory cortex	31	Asymptomatic	Asleep	Motor & sensory	NA	Total	New sensory disturbances
11	SMA	35	Weakness	Awake	Motor, sensory & SMA	NA	Total	Severe weakness
12	Motor cortex	47	Weakness	Awake	Motor, sensory & language	NA	Total	Severe weakness
13	Motor cortex	30	Seizures	Asleep	Motor & sensory	NA	Total	NA
14	Sensory cortex	37	Seizures	Asleep	Motor & sensory	NA	Total	NA
15	SMA	64	Seizures	Awake	Motor, sensory & SMA	NA	Total	NA
16	SMA	38	Seizures	Awake	Motor, sensory & SMA	NA	Total	NA
17	Motor cortex	42	Seizures	Awake	Motor, sensory & language	NA	Total	NA
18	Motor cortex	40	Seizures	Awake	Motor, sensory & language	NA	Total	NA
19	Motor cortex	46	Behavioral disturbances	Asleep	Motor & sensory	Partial motor seizure	Total	NA
20	Motor cortex	38	Seizures	Asleep	Motor & sensory	NA	Total	NA
21	Motor cortex	37	Weakness	Asleep	Motor & sensory	NA	Total	New sensory disturbances
22	Sensory cortex	37	Seizures	Asleep	Motor & sensory	NA	Total	NA
23	Motor cortex	63	Weakness	Asleep	Motor & sensory	NA	Total	NA
24	Motor cortex	30	Weakness	Asleep	Motor & sensory	NA	Subtotal	Severe weakness
25	Motor cortex	32	Headache	Asleep	Motor & sensory	NA	Total	NA
26	Motor cortex	30	Seizures	Asleep	Motor & sensory	NA	Total	NA
27	Motor cortex	37	Weakness	Asleep	Motor & sensory	NA	Total	NA
28	Motor cortex	48	Weakness	Asleep	Motor & sensory	NA	Total	NA
29	Motor cortex	32	Weakness	Asleep	Motor & sensory	NA	Subtotal	Severe weakness
30	Motor cortex	37	Weakness	Asleep	Motor & sensory	NA	Total	NA
31	Motor cortex	40	Sensory disturbances	Asleep	Motor & sensory	NA	Total	NA
32	Sensory cortex	48	Weakness	Asleep	Motor & sensory	NA	Total	NA
33	Motor cortex	50	Weakness	Awake	Motor, sensory & language	NA	Total	NA

NA = not applicable.

* Because metastases are usually subcortical lesions, we classified the location of the the metastasis as the motor cortex, sensory cortex, or SMA depending on which cortex was intersected by the line describing the shorter distance from the metastasis to the brain surface.

TABLE 3. Surgical results

Characteristic	No. (%)
Resection	
Total	31 (93.9)
Subtotal	2 (6.1)
Surgical complications	
Intraop seizure	1 (3)
Other major complications	1 (3)
Mortality	
Periop*	1 (3)

* Perioperative mortality occurred during hospital admission.

TABLE 4. Patient distribution according to KPS

KPS Score	No. of Patients (%)
Preop KPS score	
0%–40%	0 (0)
50%–70%	0 (0)
80%–100%	33 (100)
Postop KPS score	
0%–40%	1 (3.0)
50%–70%	7 (21.2)
80%–100%	25 (75.8)
6-mo follow-up KPS score	
0%–40%	7 (21.2)
50%–70%	2 (6.1)
80%–100%	24 (72.7)

and was stopped with the application of cold Ringer's lactate onto the brain cortex. The intraoperative seizure did not impede the neurophysiological monitoring and the total removal of the metastasis. The patient received anticonvulsant medication and was asymptomatic after surgery without any further seizures (Table 3). Two patients who had seizures as a presenting symptom required control of the partial seizures with anticonvulsant therapy during hospitalization. None of these patients presented new postoperative transient or permanent neurological deficits.

The overall mean postoperative KPS score was 81.5% (median 90%), which was comparable to the mean preoperative KPS score of 83.0% ($p = 0.60$). At 6 months after surgery, 17 patients showed an improvement in KPS score compared with the postoperative evaluation (Table 4). The median preoperative KPS score was 80%, while the median postoperative KPS score and median KPS score at 6 months of follow-up was 90% in both cases. Of the total patients included in the series, 15 (45.4%) patients were asymptomatic and 24 (72.7%) had a KPS score greater than 80% at 6 months. At 6 months of follow-up, 88.9% of the patients who survived had a KPS score greater than 80%.

The mean survival period of our series was 24.4 months. However, patients who worsened postoperatively had a mean survival of 13.5 months. Survival showed a statistically significant positive correlation with postoperative KPS ($r_s = 0.345$; $p < 0.05$) (Fig. 2).

Discussion

Advances in the diagnosis and treatment of various cancers have resulted in the improvement of patient survival. However, there has been a concurrent increase in the incidence of brain metastases, which are now the most frequent intracranial malignant tumor of adults. In 1990, Patchell et al. published a study in which they demonstrated the superiority of surgery followed by WBRT for the treatment of solitary brain metastasis compared with WBRT alone, effectively increasing the mean survival of patients from 15 to 40 weeks.[30] Level I evidence-based data also indicate that resection followed by postoperative WBRT is superior to WBRT alone.[18] Therefore, resection of a single metastasis is considered the standard treatment for patients with an accessible lesion, good functional status, and absent or controlled extracranial disease.[24–26,41]

Today, the debate has moved from the question of whether resection is appropriate to the question of how to best deal with lesions located in or affecting sites of high eloquence, such as the central region. Moreover, most brain metastases are located at the gray matter–white matter junction, and corticotomy is required to approach them; as they are frequently located in the rolandic region, it is necessary to establish the safest treatment option for central region metastases.[32] Due to the proximity of these tumors to the primary motor cortex, primary sensory cortex, and motor and sensory pathways, great care must be taken to prevent the development of new and permanent sensorimotor deficits after surgery. Furthermore, depending on the tumor volume, other cognitive functions could be impaired during resection, including language.

For these reasons, some authors have advocated the use of SRS as an alternative treatment to surgery.[21,44] Nevertheless, SRS has some limitations and disadvantages of its own in the treatment of brain metastases. For example, SRS does not relieve the symptoms caused by the mass effect of the tumor, edema, or hydrocephalus, does not provide a histopathological diagnosis of the lesion, and larger tumor volumes are associated with less satisfactory outcomes.[18,21] Furthermore, among patients treated with SRS, Williams et al. reported the development of new motor deficits in more than 11% of patients and emphasized the increased risk of treatment-related complications when lesions involved functional brain regions.[47] However, only a few researchers have analyzed the role of surgery for brain metastases located in the central region.[10,25,45,46] To the best of our knowledge, the present series is the largest to describe and analyze the results of surgical treatment for such tumors.

In 2011 Walter et al. described 20 patients suffering from single subcortical metastases in the central region who were surgically treated with the aid of continuous neurophysiological monitoring.[45] Gross-total resection was achieved in 95% of patients, and although 3 patients suffered a postoperative worsening of hemiparesis, this was transient in 2 patients. Walter et al. presented similar results to ours at 6-month follow-up, with 10 patients improving in the 6 months after the operation and 12 (66.7%) patients having a KPS score greater than 70%.

Recently, Kellogg et al. reported on 17 patients with cerebral metastases within the precentral gyrus who were

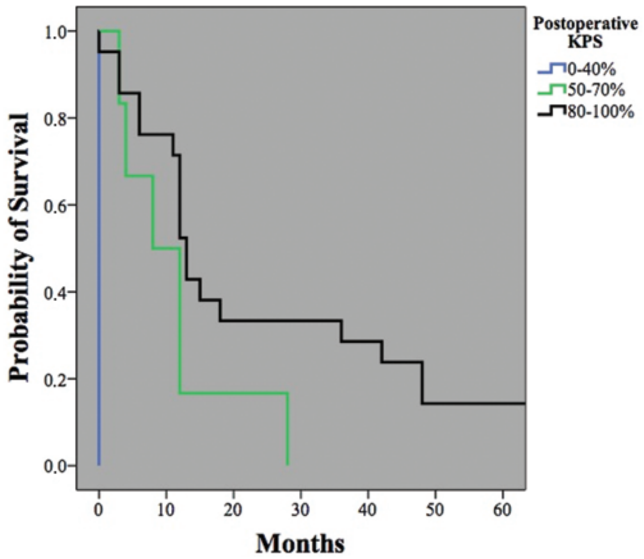

FIG. 2. Kaplan-Meier curve showing the differences in survival related to postoperative KPS among the patients during a period of 5 years. Postoperative KPS was measured at the moment of hospital discharge. Figure is available in color online only.

surgically resected without cortical mapping or stimulation.[25] The safest noneloquent route to the lesion and location for corticotomy were anatomically established intraoperatively by employing neuronavigation. Kellogg et al. reported good results with gross-total resection in all patients, improved paresis in 13 patients, and new postoperative hemiparesis that resolved partially within 3 months in 1 patient. No data on tumor relapse were available.

Image guidance during the resection of metastases could be used as an alternative to our approach, but this would be less accurate because it relies on images obtained prior to surgery that could be subject to brain shift.[17] Intraoperative brain shift—which can follow dural opening, use of mannitol or hypertonic saline, CSF drainage, or tumor resection—can be as large as 2.4 cm during tumor surgery.[27,33] Furthermore, the use of functional MRI in localizing eloquent areas has limitations, with false positives and false negatives being reported due to tumor metabolism and edema.[23,36]

In our view, the safest, most reliable method to localize eloquent brain areas, and thus to avoid damage to them during surgery, is to perform a patient-tailored functional guided approach that combines intraoperative mapping techniques with neurophysiological monitoring.[7] Together, these techniques not only provide the surgeon with information of the functionality of the underlying tissue, but they also provide the ability (e.g., by subcortical monopolar stimulation mapping) to assess the subcortical distance to the motor function pathway. Indeed, Nossek et al. compared the thresholds of subcortical monopolar mapping (a train of 5–7 stimuli, pulse duration 0.5 msec, 300 Hz) to navigation with brain shift correction by intraoperative ultrasonography. They showed a linear correlation between the distance to the CST and the threshold of subcortical stimulation producing a motor response, with a relationship of 0.97 mA for every 1 mm of brain tissue.[28] This corresponds to our rule of thumb that 1 mA was equivalent to 1 mm. This linear correlation between stimulus intensity (train of 5 stimuli, pulse duration 0.2 msec, 500 Hz) and distance was also recently postulated by Ohue et al., who analyzed the distance of the postoperative resection cavity to the imaged CST on early postoperative DTI MRI.[29]

EBS techniques performed by a trained team have been proven safe. In our series, we considered the single reported intraoperative seizure to be a mild surgical complication because it was elicited by electrical stimulation of the cerebral cortex, even though the application of cold Ringer's lactate terminated the seizure immediately. The reported seizure did not result in any other consequences and surgery continued without further problems. Therefore, consistent with previous reports, the EBS technique permitted the exact localization of function at the cortical and subcortical levels in order to establish a safe approach route to the lesion, thereby facilitating safer resection in eloquent areas. Moreover, these techniques allowed for the integrity of anatomical-functional networks to be tested and confirmed after removal of the tumor.[12]

Metastases are not sharply delimitated from the surrounding tissue as previously believed. Also, aggressive tumor metastases can infiltrate noncancerous cerebral parenchyma to a maximum depth of 1 to 3 mm,[3] exhibiting tongue-like expansion into the adjacent brain tissue that can lead to local recurrence in up to 59% of cases, despite gross-total macroscopic resection.[19] Yoo et al. extended resection to a depth of 5 mm after complete microsurgical resection of the metastases located in nonfunctional areas and compared them with a group in which resection was not extended and achieved significantly improved local tumor control.[48] Unless supramarginal resection is not an appropriate strategy for lesions located in eloquent brain areas, EBS could provide continuous feedback of the subcortical functional pathway during supramarginal resection of a noneloquent lesion when the resection reaches an eloquent area. Without the safeguards offered by EBS, the risk of unsuspected permanent neurological deficit is likely to be prohibitively high in eloquent areas.[19]

When we analyzed the correlation between preoperative functional status and the survival period it did not reach statistical significance, probably due to our selection process. Many authors have previously demonstrated a relationship between preoperative functional status and survival time, as well as the real impact of preoperative KPS on clinical outcomes.[2,24,38,41] For that reason, we excluded patients whose KPS functional status was less than 70%. Therefore, we only included patients with a high preoperative functional status. Despite this, we did find a statistically significant correlation with postoperative functional status itself and the survival period. Although the functional status of most patients improved during the follow-up period, a decrease in the postoperative status alone was associated with a negative impact on survival.

We must keep in mind that the majority of patients will die due to the progression of their primary tumor, and that a decrease in the postoperative functional status could leave the patient in a situation of dependency or decrease the treatment options available for the primary tumor. Indeed, bad functional status after surgery could mean that the patient would not be suitable for postoperative systemic therapy, which would significantly affect survival.[2]

Therefore, all reasonable efforts must be directed toward the avoidance of permanent deterioration postoperatively. The implementation of a patient-tailored functional approach to surgery for metastases of the central region offers clear advantages in the treatment of brain metastases, and is currently the most reliable method for avoiding permanent neurological deficits.

Conclusions

Intraoperative brain mapping and neurophysiological monitoring by a trained team during the resection of central-region metastases is a safe procedure that can improve surgical planning. These techniques allow the surgeon to reach the lesion and perform maximal resection while avoiding structural damage to eloquent areas and preserving crucial functional parenchyma. In turn, this reduces the chance of permanent neurological deficit and improves the functional outcome of the patient.

References

1. Al-Shamy G, Sawaya R: Management of brain metastases: the indispensable role of surgery. **J Neurooncol 92:**275–282, 2009
2. Arita H, Narita Y, Miyakita Y, Ohno M, Sumi M, Shibui S: Risk factors for early death after surgery in patients with brain metastases: reevaluation of the indications for and role of surgery. **J Neurooncol 116:**145–152, 2014
3. Baumert BG, Rutten I, Dehing-Oberije C, Twijnstra A, Dirx MJM, Debougnoux-Huppertz RMTL, et al: A pathology-based substrate for target definition in radiosurgery of brain metastases. **Int J Radiat Oncol Biol Phys 66:**187–194, 2006
4. Catani M, Mesulam MM, Jakobsen E, Malik F, Martersteck A, Wieneke C, et al: A novel frontal pathway underlies verbal fluency in primary progressive aphasia. **Brain 136:**2619–2628, 2013
5. Cedzich C, Taniguchi M, Schäfer S, Schramm J: Somatosensory evoked potential phase reversal and direct motor cortex stimulation during surgery in and around the central region. **Neurosurgery 38:**962–970, 1996
6. Chang EF, Raygor KP, Berger MS: Contemporary model of language organization: an overview for neurosurgeons. **J Neurosurg 122:**250–261, 2015
7. Fernández Coello A, Moritz-Gasser S, Martino J, Martinoni M, Matsuda R, Duffau H: Selection of intraoperative tasks for awake mapping based on relationships between tumor location and functional networks. **J Neurosurg 119:**1380–1394, 2013
8. De Witt Hamer PC, Robles SG, Zwinderman AH, Duffau H, Berger MS: Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. **J Clin Oncol 30:**2559–2565, 2012
9. Dea N, Borduas M, Kenny B, Fortin D, Mathieu D: Safety and efficacy of Gamma Knife surgery for brain metastases in eloquent locations. **J Neurosurg 113 (Suppl):**79–83, 2010
10. Duffau H: Recovery from complete hemiplegia following resection of a retrocentral metastasis: the prognostic value of intraoperative cortical stimulation. **J Neurosurg 95:**1050–1052, 2001
11. Duffau H, Capelle L, Sichez J, Faillot T, Abdennour L, Law Koune JD, et al: Intra-operative direct electrical stimulations of the central nervous system: the Salpêtrière experience with 60 patients. **Acta Neurochir (Wien) 141:**1157–1167, 1999
12. Duffau H, Lopes M, Arthuis F, Bitar A, Sichez JP, Van Effenterre R, et al: Contribution of intraoperative electrical stimulations in surgery of low grade gliomas: a comparative study between two series without (1985-96) and with (1996-2003) functional mapping in the same institution. **J Neurol Neurosurg Psychiatry 76:**845–851, 2005
13. Gabarrós A, Martino J, Juncadella M, Plans G, Pujol R, Deus J, et al: [Intraoperative identification of the supplementary motor area in neurooncological surgery.] **Neurocirugia (Astur) 22:**123–132, 2011 (Span)
14. Gabarrós A, Young WL, McDermott MW, Lawton MT: Language and motor mapping during resection of brain arteriovenous malformations: indications, feasibility, and utility. **Neurosurgery 68:**744–752, 2011
15. Gates M, Alsaidi M, Kalkanis S: Surgical treatment of solitary brain metastases. **Prog Neurol Surg 25:**74–81, 2012
16. Grant GA, Farrell D, Silbergeld DL: Continuous somatosensory evoked potential monitoring during brain tumor resection. Report of four cases and review of the literature. **J Neurosurg 97:**709–713, 2002
17. Garber ST, Jensen RL: Image guidance for brain metastases resection. **Surg Neurol Int 3 (Suppl 2):S**111–S117, 2012
18. Kalkanis SN, Kondziolka D, Gaspar LE, Burri SH, Asher AL, Cobbs CS, et al: The role of surgical resection in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. **J Neurooncol 96:**33–43, 2010
19. Kamp MA, Dibué M, Niemann L, Reichelt DC, Felsberg J, Steiger HJ, et al: Proof of principle: supramarginal resection of cerebral metastases in eloquent brain areas. **Acta Neurochir (Wien) 154:**1981–1986, 2012
20. Kronfeld-Duenias V, Amir O, Ezrati-Vinacour R, Civier O, Ben-Shachar M: The frontal aslant tract underlies speech fluency in persistent developmental stuttering. **Brain Struct Funct 221:**365–381, 2016
21. Luther N, Kondziolka D, Kano H, Mousavi SH, Flickinger JC, Lunsford LD: Motor function after stereotactic radiosurgery for brain metastases in the region of the motor cortex. **J Neurosurg 119:**683–688, 2013
22. MacDonald DB, Skinner S, Shils J, Yingling C: Intraoperative motor evoked potential monitoring—a position statement by the American Socity of Neurophysiological Monitoring. **Clin Neurophysiol 124:**2291–2316, 2013
23. Martino J, Gabarrós A, Deus J, Juncadella M, Acebes JJ, Torres A, et al: Intrasurgical mapping of complex motor function in the superior frontal gyrus. **Neuroscience 179:**131–142, 2011
24. Mintz A, Perry J, Spithoff K, Chambers A, Laperriere N: Management of single brain metastasis: a practice guideline. **Curr Oncol 14:**131–143, 2007
25. Kellogg RG, Munoz LF: Selective excision of cerebral metastases from the precentral gyrus. **Surg Neurol Int 4:**66, 2013
26. Mut M: Surgical treatment of brain metastasis: a review. **Clin Neurol Neurosurg 114:**1–8, 2012
27. Nabavi A, Black PM, Gering DT, Westin CF, Mehta V, Pergolizzi RS, et al: Serial intraoperative magnetic resonance imaging of brain shift. **Neurosurgery 48:**787–798, 2001
28. Nossek E, Korn A, Shahar T, Kanner AA, Yaffe H, Marcovici D, et al: Intraoperative mapping and monitoring of the corticospinal tracts with neurophysiological assessment and 3-dimensional ultrasonography-based navigation. Clinical article. **J Neurosurg 114:**738–746, 2011
29. Ohue S, Kohno S, Inoue A, Yamashita D, Harada H, Kumon Y, et al: Accuracy of diffusion tensor magnetic resonance imaging-based tractography for surgery of gliomas near the pyramidal tract: a significant correlation between subcortical electrical stimulation and postoperative tractography. **Neurosurgery 70:**283–294, 2012
30. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al: A randomized trial of surgery in the treatment of single metastases to the brain. **N Engl J Med 322:**494–500, 1990

31. Penfield W, Boldrey E: Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. **Brain 60:**389–443, 1937
32. Peretti-Viton P, Margain D, Murayama N, Kadr I, Peragut JC: Brain metastases. **J Neuroradiol 18:**161–172, 1991
33. Reinges MHT, Nguyen HH, Krings T, Hütter BO, Rohde V, Gilsbach JM: Course of brain shift during microsurgical resection of supratentorial cerebral lesions: limits of conventional neuronavigation. **Acta Neurochir (Wien) 146:**369–377, 2004
34. Rogne SG, Rønning P, Helseth E, Johannesen TB, Langberg CW, Lote K, et al: Craniotomy for brain metastases: a consecutive series of 316 patients. **Acta Neurol Scand 126:**23–31, 2012
35. Romstöck J, Fahlbusch R, Ganslandt O, Nimsky C, Strauss C: Localisation of the sensorimotor cortex during surgery for brain tumours: feasibility and waveform patterns of somatosensory evoked potentials. **J Neurol Neurosurg Psychiatry 72:**221–229, 2002
36. Roux FE, Boulanouar K, Lotterie JA, Mejdoubi M, LeSage JP, Berry I: Language functional magnetic resonance imaging in preoperative assessment of language areas: correlation with direct cortical stimulation. **Neurosurgery 52:**1335–1347, 2003
37. Sartorius CJ, Berger MS: Rapid termination of intraoperative stimulation-evoked seizures with application of cold Ringer's lactate to the cortex. Technical note. **J Neurosurg 88:**349–351, 1998
38. Schackert G, Lindner C, Petschke S, Leimert M, Kirsch M: Retrospective study of 127 surgically treated patients with multiple brain metastases: indication, prognostic factors, and outcome. **Acta Neurochir (Wien) 155:**379–387, 2013
39. Sierpowska J, Gabarrós A, Ripollés P, Juncadella M, Castañer S, Camins Á, et al: Intraoperative electrical stimulation of language switching in two bilingual patients. **Neuropsychologia 51:**2882–2892, 2013
40. Sills AK: Current treatment approaches to surgery for brain metastases. **Neurosurgery 57 (5 Suppl):**S24–S32, S1–S4, 2005
41. Soffietti R, Cornu P, Delattre JY, Grant R, Graus F, Grisold W, et al: EFNS Guidelines on diagnosis and treatment of brain metastases: report of an EFNS Task Force. **Eur J Neurol 13:**674–681, 2006
42. Szelényi A, Kothbauer KF, Deletis V: Transcranial electric stimulation for intraoperative motor evoked potential monitoring: Stimulation parameters and electrode montages. **Clin Neurophysiol 118:**1586–1595, 2007
43. Taniguchi M, Cedzich C, Schramm J: Modification of cortical stimulation for motor evoked potentials under general anesthesia: technical description. **Neurosurgery 32:**219–226, 1993
44. Tobler WD, Stanley M: Stereotactic resection of brain metastases in eloquent brain. **Stereotact Funct Neurosurg 63:**38–44, 1994
45. Walter J, Kuhn SA, Waschke A, Kalff R, Ewald C: Operative treatment of subcortical metastatic tumours in the central region. **J Neurooncol 103:**567–573, 2011
46. Weil RJ, Lonser RR: Selective excision of metastatic brain tumors originating in the motor cortex with preservation of function. **J Clin Oncol 23:**1209–1217, 2005
47. Williams BJ, Suki D, Fox BD, Pelloski CE, Maldaun MVC, Sawaya RE, et al: Stereotactic radiosurgery for metastatic brain tumors: a comprehensive review of complications. **J Neurosurg 111:**439–448, 2009
48. Yoo H, Kim YZ, Nam BH, Shin SH, Yang HS, Lee JS, et al: Reduced local recurrence of a single brain metastasis through microscopic total resection. **J Neurosurg 110:**730–736, 2009
49. Zhang X, Zhang W, Cao WD, Cheng G, Liu B, Cheng J: A review of current management of brain metastases. **Ann Surg Oncol 19:**1043–1050, 2012

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Sanmillan, Gabarrós. Acquisition of data: Sanmillan, Fernández-Coello, Plans. Analysis and interpretation of data: Sanmillan, Fernández-Coello, Fernández-Conejero. Drafting the article: Sanmillan. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Sanmillan. Statistical analysis: Sanmillan. Study supervision: Gabarrós.

Correspondence

Jose L. Sanmillan, Neurosurgery Department, Hospital Universitari de Bellvitge, Feixa Llarga s/n, 08907 Hospitalet de Llobregat, Barcelona, Spain. email: sanmillan.joseluis@gmail.com.