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ORIGINAL ARTICLE

# Surgery on motor area metastasis

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**Abstract** The role of surgery on central area metastasis remains unclear, and outcome data are still controversial. The aim of our study is to analyze the predictive value of clinical and surgical data on motor and functional outcome of patients, taking into account new emerging data on boundary irregularity of brain metastasis. We retrospectively analyzed 47 consecutive patients who underwent surgery assisted by neurophysiologic monitoring for a solitary metastasis in central area between 2010 and 2013. Inclusion criteria were as follows: good functional status (Karnofsky Performance Status (KPS) ≥70), controlled systemic disease, and absence of extra-cranial dissemination. At 1-month follow up, motor and functional outcomes were compared with preoperative clinical status, response to corticosteroids, extent of tumor resection, boundary irregularity, and size of tumor. Gross total resection was achieved in 93.6 % of cases. In preoperative symptomatic patients, motor outcome (according to Medical Research Council grading scale) improved in 55.5 % and worsened in 16.7 %, while functional outcome (according to KPS score) improved in 50 % and worsened in 14.2 % of cases. No worsening occurred in preoperative asymptomatic patients. Motor outcome resulted to be not correlated with preoperative deficits, tumor volume, or preoperative response to corticosteroid treatment. Remarkably, motor outcome and extent of surgical resection appeared strongly correlated with tumor boundary irregularity ($p < 0.05$). Surgery with neurophysiologic monitoring on motor area metastasis can improve functional and motor condition in selected patients. Tumor volume does not represent a limit in surgery. The high correlation between clinical outcome, resection rate, and tumor boundary irregularity strengthens a new belief on the infiltrative growing pattern of brain metastasis. Motor function was evaluated according to Medical Research Council grading scale (Ott et al. 2014) while functional status was assessed according to KPS score.

**Keywords** Brain metastasis · Central area · Neurophysiologic monitoring assisted surgery · Functional outcome · Motor outcome · Karnofsky Performance Status

## Introduction

The role of surgery in the treatment of central area metastases represents an emerging issue in the current neuro-oncological setting [1, 3, 5, 7, 14, 20, 21]. Indeed, even if boundaries of surgery have recently moved forward thanks to the intra-operative assistance of neurophysiologic monitoring and more in general by new technologies [4, 9, 15], only few data are available on the real impact of surgery on this specific subgroup of patients and on criteria of patient selection. In particular, the consequence of surgery on the functional status (Karnofsky Performance Status, KPS) of these patients has not been investigated so far. Actually, motor outcome can represent a main disability, but functional status in oncological patients is not only a pivotal element of quality of life; it

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predicts the response to adjuvant therapies and the overall survival of these patients [10, 18].

Finally, the current opinion usually considering non-infiltrating and well-delineated metastases eligible for surgery has been recently reviewed. The potential infiltrating feature of such lesions has been interestingly pointed out in up to 50 % of cases [2]. These considerations are essential when treating any secondary cerebral lesion, but especially central area metastases. The surgical meaning of this issue, specifically on tumor resection and on patient functional outcome, has not been investigated so far. The aim of our study was to analyze a consecutive series of patients who underwent resection of a metastasis located in the central area assisted by neurophysiologic monitoring. In this setting, we focused on the predictive value of both clinical and surgical data on motor and functional outcome of patients taking into account the emerging data on boundary irregularity of brain metastasis.

## Methods

### Enrollment criteria

Clinical and surgical data of patients who underwent surgical resection of a solitary metastasis located in the central region between January 2010 and December 2013 at the Department of Neurosurgery of Padua were retrospectively evaluated. In all cases, surgical treatment was the result of a multidisciplinary evaluation; clinical criteria for surgical treatment were as follows: Karnofsky Performance Status (KPS) ≥70, a controlled systemic disease, and the absence of extra-cranial dissemination [10]. Finally, only patients affected by metastasis located within or straight adjacent to the precentral gyrus and to the cortico-spinal tract (≤10 mm) were enrolled in the study. Relationship between tumor and motor pathways was retrospectively assessed by an expert neuroradiologist by means of a MRI with gadolinium performed before surgery (within 7 days). In particular, the relationship between tumor and corticospinal tract was assessed considering the closer fibers to the tumor.

### Surgical strategy

Patients were preoperatively studied through a magnetic resonance (MR) with gadolinium with volumetric sequences in order to obtain in all cases data for an anatomic intra-operative neuronavigation. Tractography and functional MRIs were performed in selected cases and charged, when available, in the neuronavigation system as well. Since, in all cases, lesions were edematous, preoperative corticosteroid (dexamethasone 16 mg/day) and antiepileptic treatment were preoperatively administrated in all patients. In all cases, a tailored craniotomy was performed on the basis of neuronavigation data. Corticectomy was customized according to neuronavigation and cortical mapping data. For functional mapping, a 5-mm-spaced-tip bipolar probe delivering a biphasic current was applied to the cortex for a period of 4 s (with a pulse frequency of 60 Hz, and a single pulse phase duration of 0.3 ms). The intensity of stimulation was determined through progressive increases by 0.5 mA until a motor response was obtained. Our surgical attitude was to perform cortical mapping from the beginning and intra-operative mapping (IOM) including tracking of motor-evoked potentials (MEPs), sensory-evoked potentials (SEPs), and continuous electroencephalography (EEG). If motor response induced by cortical stimulation was recorded, direct stimulation, both cortical and subcortical, was maintained during all procedure. Conversely, in cases in which electrostimulation did not elicit any motor response at cortical mapping and the neuronavigation planned surgical corridor did not cross through the motor area, the subcortical resection of tumor was based on IOM.

### Clinical variables

For each patient, clinical, surgical, and radiological findings were retrospectively evaluated according to clinical charts, surgical videos, and radiological images. Motor and functional status was assessed preoperatively and 1 month after surgery. Motor function was evaluated according to Medical Research Council grading scale [13] while functional status was assessed according to KPS score [6]. The postoperative outcome (motor and functional) was assessed by comparing preoperative and postoperative scores and was recorded as improved, stable, or worsened (new deficit or worsening of a preexisting deficit). Additional variables were the response to corticosteroid treatment, intra-operative seizure occurrence, tumor volume, and macroscopic intra-operative aspect of tumor boundaries. More precisely, tumors were divided in lesions with regular boundaries, when we intra-operatively found a well-demarcated tumor with clear resection margins and capsulated aspect, and lesions with irregular boundaries if the tumor presented an infiltrative shape with unclear resection margins (Figs. 1 and 2). Infiltration aspect was assessed by the macroscopical impression during microscopic resection. Tumor volume was analyzed on T1-weighted images after gadolinium administration and was set into two groups (<9 and ≥9 $cm^3$) according to the median volume calculated through an estimated spherical shape of the lesion [20]. The extent of resection was assessed by an expert neuroradiologist through the evaluation of a postoperative gadolinium MRI performed within 1 month after surgery and reported as gross total resection (GTR) or subtotal resection (STR) if resection was judged < or ≥ of 90 %, respectively. Histological specimens were analyzed by a pathologist with high experience in brain lesions.

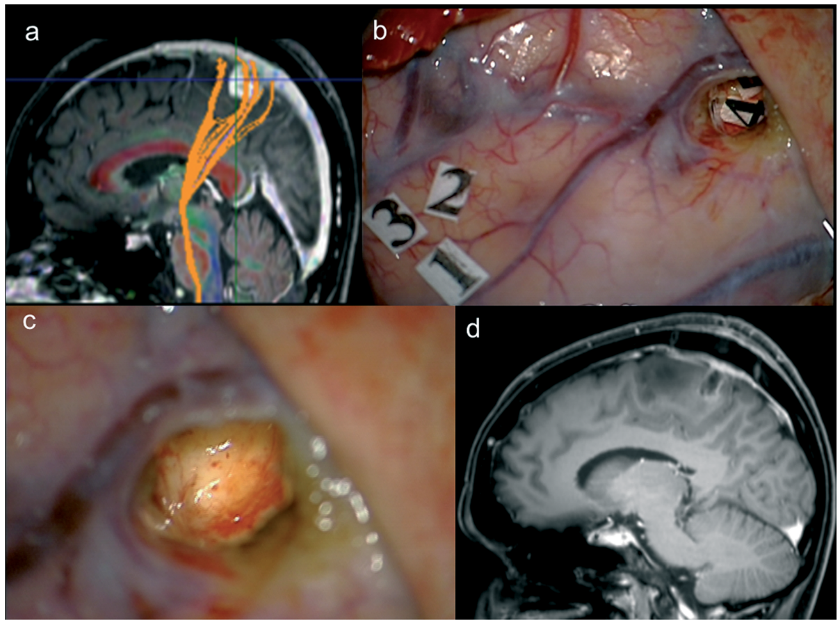


**Fig. 1** F 66/Y. **a** Preoperative DTI-MRI scan with gadolinium showing a 12-mm-sized metastasis from breast cancer in the motor area laterally surrounded by cortico-spinal tract. Intra-operative view: **b** mapping of motor area (tags *1*–*3*) and motor bundle (*4* and *5*, in the resection cavity). **c** Gross total removal at high magnification. Postoperative MRI scan with gadolinium (**d**) confirming the complete resection of tumor

## Statistical methods

Data were analyzed using the Fisher's exact test (two-sided) to compare the categorical variables with the outcome; a $p$ value $<0.05$ was considered significant.

## Ethical approval

No ethics committee approval was required for this study because it was a retrospective work concerning an intra-operative technique routinely used in our institution. Written informed consent was obtained in all patients according to hospital ethics guidelines.

# Results

## Patient population

A total of 47 patients with single metastatic lesion in central region were enrolled. Patients were 12 males and 35 females with an age range from 37 and 77 years. Preoperative symptoms were present in 32 patients (68 %) while 15 patients (32 %) revealed cerebral metastases during planned radiological follow-up without any neurological sign or symptom. In particular, motor deficits were present in 18, headache ± endocranial hypertension in 7, seizures in 5, and vertigo in 2 patients. Preoperative KPS was 100 in 20 patients and 100<

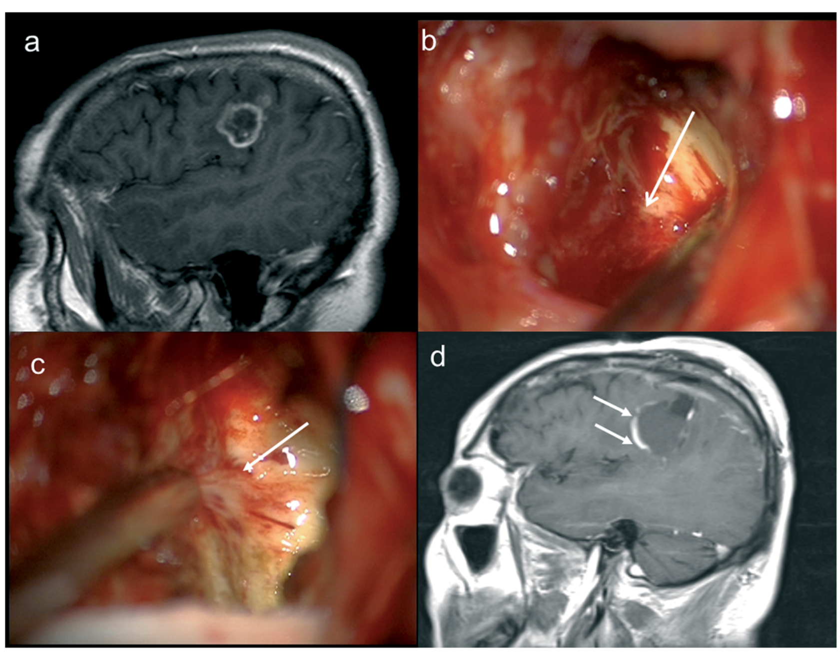


**Fig. 2** F 69/Y. **a** Preoperative T1-weighted MRI scan with gadolinium showing a 24-mm-sized metastasis from breast cancer in the motor area. Intra-operative view: The lesion shows irregular and infiltrative boundaries at medium (**b**) and high (**c**) magnification (*white arrows*). Postoperative T1-weighted MRI scan with gadolinium (**d**) showed a residual tumor enhancing after gadolinium administration (*white arrows*)

KPS≥70 in 27 cases (Table 1). Before surgery, all patients were studied with gadolinium MRI, 16 of them with a DTI, and 5 with a functional MRI. In 12 cases, tumor volume was ≥9 $cm^3$ and in 35 <9 $cm^3$. In all cases, patients had a single brain lesion with known primary disease in 38 and with unknown primary disease in 9 patients. In three cases, metastases were recurrent lesions previously irradiated. MEP/SEPP monitoring was maintained and successfully recorded in all patients, while, according to motor response elicited at cortical mapping, subcortical electrical stimulation was further kept in 14 patients (29.8 %). Intra-operative seizures were recorded only in two patients (4.2 %). Gross total resection was achieved in 44 cases (93.6 %) and subtotal resection in 3 cases (6.4 %). Histological examination on cerebral lesions confirmed 30 breast, 5 renal cell carcinoma, 5 lung, 4 melanoma, 2 colon, and 1 uterine carcinoma (Table 1). At macroscopic intra-operative aspect, tumor boundaries were found irregular with infiltrated surrounding tissue in 12 cases (25.55 %) and regular in 35 (74.46 %).

Motor deficits were present before surgery in 18 patients (38.2 %) with a preoperative KPS between 70 and 80. Conversely, 14 patients (29.8 %) presented non-focal symptoms, such as headache ± endocranial hypertension, seizures, and vertigo before surgery.

**Table 1** Demographic and clinical features of patients; non-focal sytmptoms include headache ± endocranial hypertension, seizures, and vertigo

| Factor | *N* (%) |
|---|---|
| Sex | |
| Male | 12 (25.53 %) |
| Female | 35 (74.47 %) |
| KPS | |
| 100 | 20 (42.55 %) |
| 100<KPS≥70 | 27 (57.45 %) |
| Histology | |
| Breast | 30 (63.83 %) |
| Renal cell carcinoma | 5 (10.64 %) |
| Lung | 5 (10.64 %) |
| Melanoma | 4 (8.51 %) |
| Colon | 2 (4.25 %) |
| Uterine carcinoma | 1 (2.13 %) |
| Motor deficits | 18 (38.30 %) |
| Non-focal symptoms | 14 (29.79 %) |
| Tumor volume | |
| <9 $cm^3$ | 35 (74.47 %) |
| ≥9 $cm^3$ | 12 (25.53 %) |
| Boundaries | |
| Regular | 35 (74.47 %) |
| Irregular | 12 (25.53 %) |
| Recurrences | 3 (6.38 %) |

*KPS* Karnofsky Performance Status

### Motor and functional outcome, tumor features, and rate of resection

Among the 18 patients with preoperative motor deficits, at 1-month assessment, motor function was improved in 10 (55.56 %), stable in 5 (27.78 %), and worsened in 3 (16.67 %) patients (Table 2). Overall, a transient neurological impairment was found in 17/47 patients (36.17 %) at first week after surgery assessment, but this worsening promptly recovered in 12 patients (25.53 %). Only five (10.64 %) patients experienced a permanent worse motor/functional outcome. In these patients, IONM signal decreased in four cases while, in one case, seizure occurred intra-operatively. There were no postoperative deaths.

Among the 27 patients with preoperative 100<KPS≥70, functional status improved in 59.26 % of patients (16/27). In particular, 63 % achieved a postoperative KPS of 90–100 (17/27). Conversely, a worsened KPS (60–70) was recorded in five patients, and a stable KPS compared to preoperative assessment was found in five patients. All patients with brain metastasis detected during radiological follow-up (with no symptoms and preoperative KPS of 100) presented an unchanged motor and functional outcome after surgery.

In the subgroup of patients affected by regular boundary tumors, clinical worsening occurred in 1 out of 35 cases (2.85 %) compared to 4 out of 12 patients affected by irregular boundary tumors (33.33 %) ($p = 0.011$). Gross total removal (>90 %) was achieved in 100 % of regular boundary lesions and in 75 % (9/12) of irregular boundary lesions ($p = 0.013$, Table 3).

Preoperative clinical response to corticosteroid treatment did not correlate with the outcome. However, it seemed to be more efficient in patients presenting motor deficits than in those with non-focal symptoms with an improvement rate of 44.45 % (8/18) versus 0 % (0/14) respectively ($p = 0.0044$). We also found a significant lower response to preoperative corticosteroid treatment in larger tumors compared to small ones ($p = 0.004$), and in this group of patients, we maintained both IOM and cortical mapping in a major rate ($p = 0.0001$). However, motor outcome and extent of resection resulted to be not correlated with tumor volume (Table 3).

**Table 2** One-month outcome according to preoperative clinical assessment

| | Asymptomatic | Symptomatic | | |
|---|---|---|---|---|
| | | Total (%) | Motor deficit (%) | Other deficits (%) |
| Improved | 0 | 17 (53.12 %) | 10 (55.56 %) | 7 (50 %) |
| Stable | 15 (100 %) | 10 (31.25 %) | 5 (27.78 %) | 5 (35.71 %) |
| Worsened | 0 | 5 (15.62 %) | 3 (16.67 %) | 2 (14.28 %) |

**Table 3** Relationship between tumor volume and boundaries and clinical and surgical outcome

| | <9 $cm^3$ | ≥9 $cm^3$ | *p* value | Irregular boundaries | Regular boundaries | *p* value |
|---|---|---|---|---|---|---|
| GTR | 34 | 10 | 0.156 | 9 | 35 | 0.013* |
| STR | 1 | 2 | | 3 | 0 | |
| Stable/improved at 1 month | 32 | 10 | 0.590 | 8 | 34 | 0.011* |
| Worsened/new defecit at 1 month | 3 | 2 | | 4 | 1 | |
| Preoperative deficit | 11 | 7 | 0.167 | 3 | 15 | 0.078 |
| No preoperative deficit | 24 | 5 | | 9 | 10 | |
| Improvement after corticosteroids | 8 | 0 | 0.004* | 2 | 6 | 0.558 |
| No improvement after corticosteroids | 3 | 7 | | 1 | 9 | |
| IOM+cortical mapping | 4 | 10 | 0.0001* | 4 | 10 | 0.731 |
| IOM | 31 | 2 | | 8 | 25 | |

*GTR* gross total resection, *STR* subtotal resection, *IOM* intra-operative mapping

*Significant *p* value

## Discussion

### Our present relevant results compared to pertinent literature

Nowadays, several studies compared different treatment options, but only few data concerning outcome after central area metastases surgery are available. We reviewed the most recent English literature on a large series of central area metastasis focused on this topic (Table 4). To our knowledge, this is the first study in which surgery is performed with both IOM and cortical mapping as a unique strategy.

With regard to the preoperative motor status of patients, Tan and colleagues [19] reported that no patient who was neurologically intact preoperatively deteriorated after surgery. In non-motor symptomatic patients, we found 14.28 % of worsening, compared with 22 % of the largest series of stereotactic radiosurgery (SRS) [8], and at 1-month follow-up, no outcome differences were found in patients presenting motor and non-motor symptoms. This is an encouraging data suggesting that neurophysiologic assisted surgery is a useful treatment not only for preoperatively motor-impaired patients but also for non-motor symptomatic patients with the definite advantage of tumor resection.

On the other hand, our motor and functional outcomes (KPS) show that surgical approach is feasible not only in patients with a preoperative good clinical assessment but also in patients with preoperative neurological deficits with a remarkable improvement rate of KPS score (59 %). This improvement in KPS strengthens data available from other smaller series [7, 20, 21] and plays an important meaning from an oncological point of view since it has a great impact on the response to adjuvant therapies and the overall survival [10, 18].

Series based on awake surgery showed a higher overall rate of improvement with less new/worsened deficits [17, 19, 21], probably due to a more sensitive brain mapping response [12].

Weil and co-workers [21] showed that the tumor volume did not determine any differences on motor outcome ($p>0.05$). This point has been confirmed in our experience, thus suggesting that tumor volume does not represent a limit in patient selection for surgery. The maintaining of cortical mapping in resection of these large lesions can elicit a motor response also in very compromised motor networks giving an early warning sign [5, 16]. Indeed, we found that IOM and cortical mapping were both maintained in a major rate in larger tumors than in smaller ones ($p=0.0001$). Moreover, tumor size did not correlate with resection rate or with functional outcome conversely; in SRS, larger tumors were found to be related with less satisfactory outcomes and motor deterioration [8, 21]. So, no matter the tumor volume, surgery could be considered as the main treatment option in motor area metastasis achieving radical oncologic resection with satisfactory outcome. Moreover, in the series treated with SRS by Luther and colleagues [8], improvement was achieved in 31 % compared to 36.1 % of our series and worsening occurred in 19 % versus 10.6 % of our cases. In a recent study on risks of postoperative paresis in motor eloquently located brain metastases [11], authors stressed also the significant role of radiotherapy performed before surgery leading to significantly higher risk for new postoperative motor deficits in patients with motor located brain metastases.

A new emerging additional data and interesting prognostic factor in our series is the irregularity of tumor boundaries. No surgical data comparing irregular boundaries to clinical outcome have been reported so far in literature. Our data on clinical outcome showed a strong impact and correlation of tumor infiltrating boundaries and higher rate of postoperative worsening. Additionally, the three patients with recurrences and radiation therapy history presented unclear tumor resection margins. These clinical findings seem to be strengthened by a current pathological revision on pattern of growth in brain metastases [2]. Furthermore, this model of growth resulted to be associated with the extent of surgical resection ($p=0.013$) since the only three subtotal resection in our series occurred in

**Table 4** Literature review

| Author, year | Patients[a]/ surgical procedures | Preoperatively no motor symptoms (%) | Treatment | Transient deficit (%) | Improvement (%) | Stable (%) | New/ worsened deficit (%) | GTR (%) |
|---|---|---|---|---|---|---|---|---|
| Tan TC et al., 2003 [19] | 23[a] | – | Surgery image-guided (awake surgery + cortical mapping in 83 %) | – | 83 | 13 | 4 | 92 |
| Weil RJ et al., 2005 [21] | 17[b] | 0 | Surgery with cortical mapping (awake craniotomy in 15 cases) | 17.6 | 94.2 | 0 | 5.8 | 100 |
| Shinoura N et al., 2009 [17] | 11[a] | 36.36 | Awake surgery with IOM + cortical mapping | 54.54 | 36.36 | 54.54 | 9.09 | 54.5 |
| Walter J et al., 2011 [20] | 20[a] | 45 | Surgery with IOM | 5 | 33.3 | 22.2 | 16.7 | 95 |
| Krieg SM et al., 2013 [7] | 56[a] | 44.6 | Surgery with IOM | 9 | 21 | | 12.5 | 93 |
| Luther N et al., 2013 [8] | 94[a] | – | SRS | | 31 | 50 | 19 | – |
| Present series | 47[a,b] | 31.9 | Surgery with IOM + cortical mapping | 25.5 | 36.1 | 53.2 | 10.6 | 93.3 |

Hyphen (–): not reported

*IOM* intra-operative monitoring, *SRS* stereotactic radiosurgery, *GTR* gross total resection

[a] Patients

[b] Surgical procedures

patients harboring irregular boundary lesions, while all well-demarcated lesions were completely excised (Table 3). However, in our cases, we did not find a clear correlation between irregular boundaries and specific histological primary tumor or characteristic imaging features.

## Significance of our relevant results and indications for further research

The present study shows that current neurosurgery can achieve a very high rate of complete resection of motor area metastasis usually improving motor outcome of patients. Indeed, in our series, 90 % of patients improved or remained stable after surgery, and focusing on patients with preoperative motor deficits, an improvement of preoperative motor deficit was achieved in 55 %, while only 16 % of patients developed a worsening of motor function. Even more remarkable, our data show that also the functional outcome of this challenging subgroup of patients can be improved by surgery. This issue presents remarkable implications by an oncological perspective. Indeed, this means that surgical resection of tumor not only can provide a better quality of life but also can enable patients to undergo further treatments after surgery, otherwise unsuitable.

The predictive value of preoperative clinical and surgical data on surgical outcome remains unclear. However, the absence of significant association of motor outcome with clinical features frequently presented by this subgroup of patients (such as bad motor performance and reduced functional status) suggests that surgical resection should be kept in mind even in the more challenging cases.

The most important limit of our study is represented by the strict selection of patients enrolled in the study. Indeed, criteria of selection in our series were KPS score (≥70), a controlled systemic disease, and the absence of extra-cranial dissemination. This point should be considered when approaching a patient affected by a motor area metastasis.

Irregularity of tumor boundaries of brain metastasis is an emerging issue that in our series seems to predict a worse postoperative outcome. This is an interesting issue suggested by recent pathological evidences and that must be investigated more in detail. If these data will be confirmed by further clinical studies, prediction of boundary irregularity at the preoperative stage should be pursued by modern imaging.

## Limitations of the study

The primary limitation of the current study is its retrospective nature. Certainly, future prospective studies could better define and assess the role of neurophysiologic monitoring on patient outcome comparing patients treated with and without neurophysiologic monitoring. Patients' clinical follow-up of 1 month is surely short. As a tertiary care hospital, we treat patients from other regions; however, clinical and radiological follow-up at 1 month was assessed in our institution by the same neuro-oncological team, so it was extremely homogeneous for each patient.

## Conclusions

Neurophysiologic assisted surgery of central area metastasis, in selected patients, can achieve a high rate of radical tumor resection improving both motor and functional outcomes. Irregular boundaries of tumors are strongly correlated with surgical resection rate and clinical outcome.

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## Comments

Yavor Enchev, Varna, Bulgaria

The authors retrospectively analyzed their own series of 47 consecutive patients with solitary metastatic lesions in motor area. The patients were included in the study based on strict enrollment criteria (KPS ≥70, absence of extracranial metastases and controlled systemic disease) and the tumours were resected with the assistance of neuronavigation and neurophysiologic monitoring. The motor and functional surgical outcome were evaluated and compared with the preoperative state. Based on their results, between their mostly confirmative data, the authors noted something very interesting, namely that the motor outcome and the extent of tumour resection strongly correlated with the so-called "tumour margins irregularity". By my opinion, further studies focused on defining the criteria for tumour margins irregularity, evaluating its degree of expression and eventually its potential prognostic value for the extent of surgical resection and motor outcome, are recommended.

Fumio Yamaguchi, Tokyo, Japan

Rossetto et al. reported the utilization of brain mapping technique in the removal of metastatic brain tumors. As a nature of metastatic tumors, boundaries are macroscopically clear in most cases and easy to remove without damaging adjacent neural structure. However, as the authors discussed, it is difficult to remove the tumor in case of irregular tumor margin, resulting in subtotal removal or complete removal with postoperative neurological deteriorations in eloquent areas. If the invaded brain tissue includes any eloquent fibers, the decision of removal extent must be carefully made according to intraoperative brain mapping. Also, resection of the surrounding white matter is important to prevent local recurrence. Based on this concept, tractography integrated in neuronavigation system in conjunction with intraoperative brain mapping should be used routinely in case of tumors in eloquent brain even if tumor boundaries are clear. The resection of metastatic brain tumor may be considered simple and relatively easy surgery, however, the prevention of postoperative neurological deterioration should be set high value on for patients who have limited remaining days. From this point of view intraoperative mapping is very important and essential technique.