Recovery of long-term paresis following resection of WHO grade II gliomas infiltrating the pyramidal pathway

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Running-head title: Recovery paresis motor glioma

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Abbreviations used in this paper: DTI = diffusion tensor imaging; FLAIR = fluid-attenuated inversion recovery; GIIG = World Health Organization grade II glioma; IES = intraoperative electrical stimulation; MRI = magnetic resonance imaging.

Abstract

Recent publications had reported high rates of preoperative neurological impairments in WHO grade II gliomas (GIIG) that significantly affect the quality of life. Consequently, one step further in the analysis of surgical outcome in GIIG is to evaluate if surgery is capable to improve preoperative deficits.

Here are reported two cases of GIIG infiltrating the primary motor cortex and pyramidal pathway that had a long-term paresis before surgery. Both patients were operated with intraoperative electrical stimulation mapping, with identification and preservation of the primary motor cortex and pyramidal tract. Despite the long-lasting paresis, both cases had a significant improvement of motor function after surgery.
Knowledge of this potential recovery before surgery is of major significance for planning the surgical strategy in GIIG. Two possible predictors of motor recovery were analyzed: 1) Reconstruction of the corticospinal tract with diffusion tensor imaging tractography is indicative of anatomo-functional integrity, despite tract deviation and infiltration. 2) Intraoperative identification of motor response by electrostimulation confirms the presence of an intact peritumoral tract. Thus, resection should stop at this boundary even in cases of long lasting preoperative hemiplegia.

Introduction

World Health Organization grade II gliomas (GIIG) are slow growing tumors that diffusely infiltrate the brain. Surgery in nowadays considered as an efficient initial treatment, i.e. with an impact on the anaplastic transformation and survival. GIIG are known to frequently involve functional regions. During resection of these tumors located within eloquent areas, intraoperative electrical stimulation (IES) mapping has proven to be an essential tool, as it enables to maximize the extent of the resection and decrease the risk of permanent deficits.

It has been traditionally considered that GIIG patients exhibit a completely normal clinical examination before treatment. However, recent publications with extensive neuropsychological evaluations had reported high rates of cognitive impairment that significantly affect the quality of life. Consequently, one step further in the analysis of surgical outcome is to evaluate if IES surgery is also capable to improve preoperative deficits.
Here are reported two cases of GIIG infiltrating the primary motor cortex and pyramidal pathway that had a long-term paresis before surgery. Long-term deficits are normally indicative of a definitive neural lesion, and are thought to be irreversible. However, the two cases presented here had a significant improvement of motor function after surgery. Knowledge of this potential recovery before surgery is of major significance for planning the surgical strategy in GIIG, as this can define aspects such as if surgery is possible or not, and the exact quantification of risks and benefits. Our main interest was to analyze possible predictors of motor recovery after surgery. Specifically, we focused in neuroimaging and surgical factors that may anticipate good functional outcome.

Cases presentation

All participants gave their informed consent to participate in the research; all procedures were approved by the Hospital Universitario Marqués de Valdecilla Committee of Human Research, and all research were conducted according to the Declaration of Helsinki.

Case 1

A 37-years-old right-handed man diagnosed in August 2007 of a left frontoparietal tumor. The patient was operated in February 2008 without IES mapping, and the histopathology evidenced gemistocitic GIIG. Postoperatively, the patient had a normal neurological examination, and a MRI performed in June 2008 revealed partial tumor resection. Diffusion tensor imaging (DTI) tractography revealed that the left
pyramidal pathway had a normal anatomical location, orientation and anisotropy when compared to the contralateral side (Fig. 1). Our group has previously published the DTI tractography methodology used here for tract reconstruction (Martino, 2013 #37845). The tumor recurred in May 2009, with right hemiparesis and seizures worsening. In June 2009, the patient was treated with conformational radiotherapy (60 Gy for 34 days) and chemotherapy (Temozolamide). However, the clinical situation progressively worsened, and by September 2009 the patient already had a right hemiplegia, mild dysphasia, and medical refractory epilepsy (despite the use of four antiepileptic drugs). MRI revealed a tumor that infiltrated the Rolandic cortex and the pyramidal pathway, with a volume of 101 ml. The tumor also had a cyst in the posterior margin with nodular contrast enhancement (Fig. 2). fMRI during imaginary movement of the right hand evidenced activation of the right precentral gyrus (Fig. 2). DTI tractography revealed that the left pyramidal pathway was deviated posteriorly, and the anisotropy was reduced when compared to the contralateral side (Fig. 1). Other tracts related to motor function (subcallosal fasciculus, frontal aslant tract, cingulum, and corpus callosum) had a normal anatomical location, orientation and anisotropy (Fig. 2).

The patient was operated 80 days after the instauration of the right hemiplegia. Surgery was performed with IES mapping, with the same asleep-awake-asleep methodology previously described by our group (Martino, 2013 #37831; Martino, 2013 #37845). Stimulation of the precentral gyrus induced motor response in the right upper limb (Fig. 2). During subcortical stimulation motor responses were not elicited, so resection was extended posteriorly until eloquent cortical areas were encountered (Fig. 2). Specific motor and language rehabilitation was provided after surgery. Fifteen days after surgery the patient started to move the right upper limb, and one month later
started to move the right lower limb. The patient progressively improved motor function, and six months after surgery the medical research council muscle testing scale was as follows: proximal right arm 4/5, distal right arm 1/5, proximal right leg 4/5, distal right leg 2/5. The patient was able to walk independently with a cane and a brace in the right leg. No seizures were reported after surgery, so the antiepileptic drugs were progressively withdrawal, so one year after surgery the patient was in class I of the epilepsy outcome classification of the International League Against Epilepsy (ILAE) {Wieser, 2001 #37730}. Histopathology evidenced anaplastic glioma with gemistocytic component. MRI performed 3 months after surgery evidenced a 22 ml tumor residue (so the extent of resection was 78%). Postoperative DTI tractography revealed that the motor pathway had recovered the normal position and improved anisotropy (Fig. 1). fMRI during right hand movement evidenced activation of the right precentral gyrus (Fig. 2).

Case 2

A 29-years-old right-handed man that presented in December 2004 with a partial motor seizure. MRI revealed a lesion characteristic of a GIIG located at the left superior frontal gyrus. The tumor volume at this time was 10 ml. A “wait and see” policy was initially considered, so the patient was followed with annual MRI. By February 2007 the patient had a normal neurological examination, and MRI performed at that time with DTI tractography revealed that the left pyramidal pathway had a normal anatomical location, orientation and anisotropy when compared to the contralateral side (Fig. 3). In 2010, the clinical situation progressively worsened, and by December 2010 the patient had a moderate paresis (2/5) of the right foot. The patient also had medical
refractory epilepsy with one clonic partial seizures of the right foot a month. A MRI
performed in April 2011 revealed that the tumor had grown significantly (42 ml), with
extension to the precentral gyrus and cingulum (Fig. 4). fMRI during movement of the
right leg evidenced activation of the left precentral gyrus (Fig. 4). DTI tractography
revealed that the left pyramidal pathway was deviated posteriorly, and the
anisotropy was reduced when compared to the contralateral side (Fig. 3). Other
tracts related to motor function (subcallosal fasciculus, frontal aslant tract,
cingulum, and corpus callosum) had a normal anatomical location, orientation and
anisotropy (Fig. 4).

The patient was operated 180 days after the instauration of the paresis of the
right foot. Surgery was performed with IES mapping and an asleep-awake-asleep
technique. Sensorimotor mapping identified the motor cortex of the right arm and
face, and the sensory cortex of the right arm. An area of speech arrest was identified at
the ventral premotor cortex (Fig. 4). Direct stimulation at the subcortical level induced
motor movement of the right arm and leg (Fig. 4). Specific motor rehabilitation was
provided after surgery. Thirty days after surgery the patient started to recover the
strength in the right foot, and six months later it was completely recovered. The seizures
situation remained unchanged. Histopathology evidenced low-grade
oligodendroglioma. MRI performed 3 months after surgery evidenced a 6 ml tumor
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that the motor pathway had recovered the normal position and anisotropy (Fig. 3).
fMRI during right foot movement evidenced activation of the left precentral gyrus at
the mesial frontal lobe and at the contralateral supplementary motor area (Fig. 4).

Discussion
The presence of neurological deficits prior to surgery is an important factor for planning the surgical strategy in GIIG. In the second case presented here the patient had a long-term complete hemiplegia before surgery. Based on this information the surgeon may have considered attempting gross total resection without undue concern for preserving the motor pathway. However, despite the long-term deficit the pyramidal pathway was still functional in this case. Knowledge of this potential recovery is of major significance for preoperative planning by informing the surgeon that the pyramidal pathway is still functional, thus allowing for adaptation of the surgical strategy to identify and preserve this tract. In the present cases we analyzed the potential predictors of motor recovery after surgery.

The first factor to analyze is the relationship between the tumor and the pyramidal pathway. In the two cases presented here the pyramidal pathway was displaced by the tumor mass and the fractional anisotropy was reduced within the tract prior to surgery. Previous studies had classified the patterns of white matter tract alterations based on the anisotropy, direction and deviation. 1) Deviation: white matter tracts are displaced by the tumoral mass with normal anisotropy. 2) Infiltration: tumor infiltration of the tract that reduces anisotropy but retain enough directional organization to remain identifiable on directional DTI maps. 3) Disruption: the tract is disrupted to the point where diffusion anisotropy is lost completely. When the third pattern is present no special care need to be taken during resection to preserve the tract as it was already interrupted. In the cases presented here the corticospinal tracts were both deviated and infiltrated.

Tract deviation and deformation is due to bulk mass displacement. Tumor compression of the primary motor area may cause vascular phenomena, responsible for
dysfunction of the pyramidal cells, but without definitive destruction of these networks. Indeed, the recovery of motor function after surgery was associated to a reduction of deviation in the motor pathway. Consequently, the improvement was presumably due to the elimination of pressure on the corticospinal tract and restoration of normal perfusion. The analysis of DTI tractography and clinical examination long before worsening are in favor of this hypothesis. At this time, both patients had a normal neurological examination, and DTI tractography revealed that the pyramidal pathway had a normal anatomical location, orientation and anisotropy when compared to the contralateral side (Fig. 1 and 3). The analysis of the direction of tract displacement is important for surgery planning as it allows for adaptation of the surgical corridor to avoid destruction of the bundles. In the two cases presented here the motor pathway was displaced posteriorly, so the tumor was approached from a frontal direction, allowing for aggressive resection of the anterior portion of the tumor while avoiding the posteriorly deviated motor fibers.

In the two cases presented the pyramidal tract anisotropy was reduced preoperatively, and after surgery the tract anisotropy raised while motor strength improved. Diffuse gliomas have an infiltrative pattern, and tumor cells insinuate themselves between individual fibers without disrupting their directional organization. Tumor infiltration of the tract reduces anisotropy and may be responsible for dysfunction of the pyramidal cells. However, the patients were operated with IES mapping, and resection was pursued until motor response were found, leaving a tumor residue when invading the motor pathway. Consequently, postoperative improvement of anisotropy cannot be explained by the extirpation of the tumor cells that invaded the motor pathway. Vasogenic edema is characteristic of high-grade tumors, but may also appear in GGII with significant mass effect. Consequently, in the cases presented here
edema surrounding the tumor mass may have had an important role in the restoration of normal anisotropy after surgery. Edema is generated at the margins of the tumor mass where high pressure is transmitted to the adjacent white matter; the edema infiltrates the tracts reducing anisotropy while retaining sufficiently ordered structure to allow its identification on directional color maps. Tumor surgical removal resulted in a release of mass effect with reduction of edema and normalization of anisotropy.

Recent publications had reported that tumor morphology and subcortical tumor infiltration are important factors to predict functional recovery and extent of tumor resection in gliomas within eloquent areas. In the first case presented there was a cystic lesion that compressed the pyramidal pathway. This compression probably had an important role in the development of preoperative paresis, and the surgical decompression in postoperative recovery. However, as demonstrated by postoperative MRI, there was also an infiltrative component of the tumor that extended within the precentral gyrus and pyramidal pathway. The extent of resection in this case was defined by intraoperative electrical stimulation results, as resection was pursued until eloquent areas were encountered at the precentral gyrus.

The human motor system comprises multiple areas and connections that are involved in different aspects of executing motor tasks. Consequently, other regions different to the pyramidal pathway may have had a role in postoperative motor recovery. The supplementary motor area (SMA) is implicated in the initiation of movement and speech. When this area is injured, a SMA syndrome occurs with a reduction in spontaneous movement contralateral to the lesion while automatic movements are relatively preserved. Most of these symptoms are transient, and a rapid recovery occurs within two to four weeks. The SMA is connected to the subcallosal fasciculus and the frontal aslant tract. The subcallosal fasciculus connects the SMA to
the striatum. The frontal aslant tract has recently been described as an oblique bundle that connects the most posterior part of Broca’s territory (i.e., pre-central cortex and pars opercularis) in the inferior frontal gyrus to the SMA. Tumor infiltration of the SMA does not seem to explain the clinical course of the cases presented here. First, because the preoperative clinical pattern and the recovery pattern was not typical of a SMA syndrome as classically described. Preoperatively, both voluntary and automatic movements were impaired. The pattern of recovery after surgery was not typical of a SMA syndrome, with progressive recovery along a six months period of intensive rehabilitation. Second, the anatomical location, orientation and anisotropy of the subcallosal fasciculus and frontal aslant tract were similar before and after surgery (Fig. 3). However, it is also important to mention that structural integrity revealed with DTI tractography is not equivalent to functional integrity. Other brain mapping techniques such as transcranial magnetic stimulation will probably shed some light in the functional role of these connections within the motor circuitry, and the recovery after a lesion.

Finally, intraoperative identification of motor response by electro stimulation is an important predictive factor of recovery. In the current cases, despite the long-term paresis IES of the primary motor cortex at the damaged hemisphere was able to generate motor responses. This data indicates that the electrical impulse is transmitted from the cortex to the impaired hemibody, consequently is interpreted as an undeniable proof of the anatomo-functional integrity of the corticospinal tract. Therefore, a positive response seems to represent a valuable prognostic indicator of the potential motor recovery. Duffau has previously reported the prognostic value of IES mapping to predict functional outcome. The author describes a case of a retrocentral metastasis with intratumoral bleeding and acute complete hemiplegia. Emergency surgery was performed and IES elicited motor response at the primary motor cortex. The patient
recovered almost completely within one week. The important difference with the cases presented here is that our patients recovered motor function after a long-term motor deficit. The presences of long lasting deficits prior to surgery are indicative of a definitive lesion and are thought to be irreversible. Our findings questions at a fundamental level this established view, indicating a remarkable potential recovery of the primary motor system. Our findings have important implications for surgical planning. If motor responses are elicited at the primary motor area the resection should stop at this boundary even in cases of long lasting preoperative hemiplegia.

**Conclusions**

In GIIG infiltrating the rolandic cortex and the pyramidal pathway, a long-term motor deficit is not indicative of a definitive paresis. Surgery has the potential to release tumor compression to the motor areas with restoration of the normal function. Identification of potential indicators of motor recovery after surgery are of major significance for surgical planning. Here, two possible predictors were identified: 1) Preoperative DTI tractography is a powerful tool to evaluate tract integrity. Reconstruction of the corticospinal tract is indicative of anatomo-functional integrity, despite tract deviation and infiltration. The preoperative depiction of the direction of tract displacement is important for adaptation of the surgical corridor to avoid destruction of the bundles. 2) Intraoperative identification of motor response by electrostimulation confirms the presence of an intact peritumoral tract. Thus, if motor responses are elicited at the primary motor area the resection should stop at this boundary even in cases of long lasting preoperative hemiplegia.

Recent publications had reported high rates of language and memory deficits in
GIIG before treatment, with deterioration of the quality of life\textsuperscript{4,5}. We raise the question if surgery has also the potential to improve these complex cognitive functions. Future studies using a larger number of subjects may bear insight in this interesting issue.

**Disclosure**

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


**Figure 1**. Case 1. **A)** Magnetic resonance imaging (MRI) with diffusion tensor imaging (DTI) tractography performed in 2008, when the patient had a normal neurological examination. At this time the left pyramidal pathway had a normal anatomical location, orientation and anisotropy when compared to the contralateral side. **B)** MRI with DTI tractography performed in September 2009, when the patient had a right hemiplegia. At this time the left pyramidal pathway was deviated posteriorly by the enlarged tumor mass. **C)** MRI with DTI tractography performed in June 2010, when the patient had improve motor function in the right upper and lower limb. The patient was able to walk independently with a cane and a brace in the right leg. At this time the left pyramidal pathway had recovered the normal position and improved anisotropy.
**Figure 2.** Case 1. A) Preoperative functional magnetic resonance imaging (fMRI) obtained during imaginary movement of the right hand, demonstrating activity predominantly located in the right precentral gyrus. B) Postoperative fMRI obtained during movement of the right hand, demonstrating activity predominantly located in the right precentral gyrus. C) Preoperative sagittal T1-weighted MRI with diffusion tensor imaging (DTI) tractography reconstruction of the tracts related to motor function: subcallosal fasciculus (1), frontal aslant tract (2), cingulum (3), and corpus callosum(4). Tumor (T). D) Postoperative sagittal T1-weighted MRI with DTI tractography reconstruction of the tracts related to motor function: subcallosal fasciculus (1), frontal aslant tract (2), cingulum (3), and corpus callosum(4). Tumor (T). E) Intraoperative photograph taken before tumor resection showing the tumor margins identified with neuronavigation and marked with a yellow line. The following responses were elicited: red label with number 1 = motor response in the right upper limb; flags = language responses. F) Intraoperative photograph taken after tumor resection. The functional motor and language areas identified have been preserved.

**Figure 3.** Case 2. A) Magnetic resonance imaging (MRI) with diffusion tensor imaging (DTI) tractography performed in 2007, when the patient had a normal neurological examination. At this time the left pyramidal pathway had a normal anatomical location, orientation and anisotropie when compared to the contralateral side. B) MRI with DTI tractography performed in April 2011, when the patient had a moderate paresis (2/5) of the right foot. At this time the left pyramidal pathway was deviated posteriorly by the enlarged tumor mass. C) MRI with DTI tractography performed in September 2012, when the patient was completely recovered from the right foot paresis. At this time the left pyramidal pathway had recovered the normal position and anisotropy.
Figure 4. Case 2. A) Preoperative functional magnetic resonance imaging (fMRI) obtained during movement of the right leg, demonstrating activity predominantly located in the left precentral gyrus. B) Postoperative fMRI obtained during movement of the right leg, demonstrating activity predominantly located in the left precentral gyrus at the mesial frontal lobe and at the contralateral supplementary motor area. C) Preoperative sagittal T1-weighted MRI with diffusion tensor imaging (DTI) tractography reconstruction of the tracts related to motor function: subcallosal fasciculus (1), frontal aslant tract (2), cingulum (3), and corpus callosum (4). Tumor (T). D) Postoperative sagittal T1-weighted MRI with DTI tractography reconstruction of the tracts related to motor function: subcallosal fasciculus (1), frontal aslant tract (2), cingulum (3), and corpus callosum (4). Tumor (T). E) Intraoperative photograph taken before tumor resection showing the tumor margins identified with neuronavigation and marked with a yellow line. The following responses were elicited: red labels = motor responses in the right upper limb and face; blue labels = sensory responses in the right upper limb; flag = speech arrest. F) Intraoperative photograph taken after tumor resection. The functional motor and language areas identified have been preserved. Direct stimulation at the subcortical level induced motor movement of the right arm and leg (marked with red labels).
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Abstract

Recent publications had reported high rates of preoperative neurological impairments in WHO grade II gliomas (GIIG) that significantly affect the quality of life. Consequently, one step further in the analysis of surgical outcome in GIIG is to evaluate if surgery is capable to improve preoperative deficits.

Here are reported two cases of GIIG infiltrating the primary motor cortex and pyramidal pathway that had a long-term paresis before surgery. Both patients were operated with intraoperative electrical stimulation mapping, with identification and preservation of the primary motor cortex and pyramidal tract. Despite the long-lasting paresis, both cases had a significant improvement of motor function after surgery.
Knowledge of this potential recovery before surgery is of major significance for planning the surgical strategy in GIIG. Two possible predictors of motor recovery were analyzed: 1) Reconstruction of the corticospinal tract with diffusion tensor imaging tractography is indicative of anatomo-functional integrity, despite tract deviation and infiltration. 2) Intraoperative identification of motor response by electrostimulation confirms the presence of an intact peritumoral tract. Thus, resection should stop at this boundary even in cases of long lasting preoperative hemiplegia.

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World Health Organization grade II gliomas (GIIG) are slow growing tumors that diffusely infiltrate the brain. Surgery in nowadays considered as an efficient initial treatment, i.e. with an impact on the anaplastic transformation and survival. GIIG are known to frequently involve functional regions. During resection of these tumors located within eloquent areas, intraoperative electrical stimulation (IES) mapping has proven to be an essential tool, as it enables to maximize the extent of the resection and decrease the risk of permanent deficits.

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**Cases presentation**

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**Case 1**

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The patient was operated 80 days after the instauration of the right hemiplegia. Surgery was performed with IES mapping, with the same asleep-awake-asleep methodology previously described by our group. Stimulation of the precentral gyrus induced motor response in the right upper limb (Fig. 2). During subcortical stimulation motor responses were not elicited, so resection was extended posteriorly until eloquent cortical areas were encountered (Fig. 2). Specific motor and language rehabilitation was provided after surgery. Fifteen days after surgery the patient started to move the right upper limb, and one month later started to move the right lower limb. The patient
progressively improved motor function, and six months after surgery the medical research council muscle testing scale was as follows: proximal right arm 4/5, distal right arm 1/5, proximal right leg 4/5, distal right leg 2/5. The patient was able to walk independently with a cane and a brace in the right leg. No seizures were reported after surgery, so the antiepileptic drugs were progressively withdrawal, so one year after surgery the patient was in class I of the epilepsy outcome classification of the International League Against Epilepsy (ILAE). Histopathology evidenced anaplastic glioma with gemistocitic component. MRI performed 3 months after surgery evidenced a 22 ml tumor residue (so the extent of resection was 78%). Postoperative DTI tractography revealed that the motor pathway had recovered the normal position and improved anisotropy (Fig. 1). fMRI during right hand movement evidenced activation of the right precentral gyrus (Fig. 2).

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performed in April 2011 revealed that the tumor had grown significantly (42 ml), with extension to the precentral gyrus and cingulum (Fig. 4). fMRI during movement of the right leg evidenced activation of the left precentral gyrus (Fig. 4). DTI tractography revealed that the left pyramidal pathway was deviated posteriorly, and the anisotropy was reduced when compared to the contralateral side (Fig. 3). Other tracts related to motor function (subcallosal fasciculus, frontal aslant tract, cingulum, and corpus callosum) had a normal anatomical location, orientation and anisotropy (Fig. 4).

The patient was operated 180 days after the instauration of the paresis of the right foot. Surgery was performed with IES mapping and an asleep-asleep-asleep technique. Sensorimotor mapping identified the motor cortex of the right arm and face, and the sensory cortex of the right arm. An area of speech arrest was identified at the ventral premotor cortex (Fig. 4). Direct stimulation at the subcortical level induced motor movement of the right arm and leg (Fig. 4). Specific motor rehabilitation was provided after surgery. Thirty days after surgery the patient started to recover the strength in the right foot, and six months later it was completely recovered. The seizures situation remained unchanged. Histopathology evidenced low-grade oligodendroglioma. MRI performed 3 months after surgery evidenced a 6 ml tumor residue, so the extent of resection was 86%. Postoperative DTI tractography revealed that the motor pathway had recovered the normal position and anisotropy (Fig. 3). fMRI during right foot movement evidenced activation of the left precentral gyrus at the mesial frontal lobe and at the contralateral supplementary motor area (Fig. 4).

Discussion
The presence of neurological deficits prior to surgery is an important factor for planning the surgical strategy in GIIG. In the second case presented here the patient had a long-term complete hemiplegia before surgery. Based on this information the surgeon may have considered attempting gross total resection without undue concern for preserving the motor pathway. However, despite the long-term deficit the pyramidal pathway was still functional in this case. Knowledge of this potential recovery is of major significance for preoperative planning by informing the surgeon that the pyramidal pathway is still functional, thus allowing for adaptation of the surgical strategy to identify and preserve this tract. In the present cases we analyzed the potential predictors of motor recovery after surgery.

The first factor to analyze is the relationship between the tumor and the pyramidal pathway. In the two cases presented here the pyramidal pathway was displaced by the tumor mass and the fractional anisotropy was reduced within the tract prior to surgery. Previous studies had classified the patterns of white matter tract alterations based on the anisotropy, direction and deviation. 1) Deviation: white matter tracts are displaced by the tumoral mass with normal anisotropy. 2) Infiltration: tumor infiltration of the tract that reduces anisotropy but retain enough directional organization to remain identifiable on directional DTI maps. 3) Disruption: the tract is disrupted to the point where diffusion anisotropy is lost completely. When the third pattern is present no special care need to be taken during resection to preserve the tract as it was already interrupted. In the cases presented here the corticospinal tracts were both deviated and infiltrated.

Tract deviation and deformation is due to bulk mass displacement. Tumor compression of the primary motor area may cause vascular phenomena, responsible for dysfunction of the pyramidal cells, but without definitive destruction of these networks.
Indeed, the recovery of motor function after surgery was associated to a reduction of deviation in the motor pathway. Consequently, the improvement was presumably due to the elimination of pressure on the corticospinal tract and restoration of normal perfusion. The analysis of DTI tractography and clinical examination long before worsening are in favor of this hypothesis. At this time, both patients had a normal neurological examination, and DTI tractography revealed that the pyramidal pathway had a normal anatomical location, orientation and anisotropy when compared to the contralateral side (Fig. 1 and 3). The analysis of the direction of tract displacement is important for surgery planning as it allows for adaptation of the surgical corridor to avoid destruction of the bundles. In the two cases presented here the motor pathway was displaced posteriorly, so the tumor was approached from a frontal direction, allowing for aggressive resection of the anterior portion of the tumor while avoiding the posteriorly deviated motor fibers.

In the two cases presented the pyramidal tract anisotropy was reduced preoperatively, and after surgery the tract anisotropy raised while motor strength improved. Diffuse gliomas have an infiltrative pattern, and tumor cells insinuate themselves between individual fibers without disrupting their directional organization. Tumor infiltration of the tract reduces anisotropy and may be responsible for dysfunction of the pyramidal cells. However, the patients were operated with IES mapping, and resection was pursued until motor response were found, leaving a tumor residue when invading the motor pathway. Consequently, postoperative improvement of anisotropy cannot be explained by the extirpation of the tumor cells that invaded the motor pathway. Vasogenic edema is characteristic of high-grade tumors, but may also appear in GII with significant mass effect. Consequently, in the cases presented here edema surrounding the tumor mass may have had an important role in the restoration of
normal anisotropy after surgery. Edema is generated at the margins of the tumor mass where high pressure is transmitted to the adjacent white matter; the edema infiltrates the tracts reducing anisotropy while retaining sufficiently ordered structure to allow its identification on directional color maps. Tumor surgical removal resulted in a release of mass effect with reduction of edema and normalization of anisotropy.

Recent publications had reported that tumor morphology and subcortical tumor infiltration are important factors to predict functional recovery and extent of tumor resection in gliomas within eloquent areas. In the first case presented there was a cystic lesion that compressed the pyramidal pathway. This compression probably had an important role in the development of preoperative paresis, and the surgical decompression in postoperative recovery. However, as demonstrated by postoperative MRI, there was also an infiltrative component of the tumor that extended within the precentral gyrus and pyramidal pathway. The extent of resection in this case was defined by intraoperative electrical stimulation results, as resection was pursued until eloquent areas were encountered at the precentral gyrus.

The human motor system comprises multiple areas and connections that are involved in different aspects of executing motor tasks. Consequently, other regions different to the pyramidal pathway may have had a role in postoperative motor recovery. The supplementary motor area (SMA) is implicated in the initiation of movement and speech. When this area is injured, a SMA syndrome occurs with a reduction in spontaneous movement contralateral to the lesion while automatic movements are relatively preserved. Most of these symptoms are transient, and a rapid recovery occurs within two to four weeks. The SMA is connected to the subcallosal fasciculus and the frontal aslant tract. The subcallosal fasciculus connects the SMA to the striatum. The frontal aslant tract has recently been described as an oblique bundle
that connects the most posterior part of Broca’s territory (i.e., pre-central cortex and pars opercularis) in the inferior frontal gyrus to the SMA \cite{14, 15}. Tumor infiltration of the SMA does not seem to explain the clinical course of the cases presented here. First, because the preoperative clinical pattern and the recovery pattern was not typical of a SMA syndrome as classically described. Preoperatively, both voluntary and automatic movements were impaired. The pattern of recovery after surgery was not typical of a SMA syndrome, with progressive recovery along a six months period of intensive rehabilitation. Second, the anatomical location, orientation and anisotropy of the subcallosal fasciculus and frontal aslant tract were similar before and after surgery (Fig. 3). However, it is also important to mention that structural integrity revealed with DTI tractography is not equivalent to functional integrity. Other brain mapping techniques such as transcranial magnetic stimulation will probably shed some light in the functional role of these connections within the motor circuitry and the recovery after a lesion.

Finally, intraoperative identification of motor response by electro stimulation is an important predictive factor of recovery. In the current cases, despite the long-term paresis IES of the primary motor cortex at the damaged hemisphere was able to generate motor responses. This data indicates that the electrical impulse is transmitted from the cortex to the impaired hemibody; consequently is interpreted as an undeniable proof of the anatomofunctional integrity of the corticospinal tract. Therefore, a positive response seems to represent a valuable prognostic indicator of the potential motor recovery. Duffau has previously reported the prognostic value of IES mapping to predict functional outcome \cite{25}. The author describes a case of a retrocentral metastasis with intratumoral bleeding and acute complete hemiplegia. Emergency surgery was performed and IES elicited motor response at the primary motor cortex. The patient recovered almost completely within one week. The important difference with the cases
presented here is that our patients recovered motor function after a long-term motor deficit. The presences of long lasting deficits prior to surgery are indicative of a definitive lesion and are thought to be irreversible. Our findings questions at a fundamental level this established view, indicating a remarkable potential recovery of the primary motor system. Our findings have important implications for surgical planning. If motor responses are elicited at the primary motor area the resection should stop at this boundary even in cases of long lasting preoperative hemiplegia.

**Conclusions**

In GIIG infiltrating the rolandic cortex and the pyramidal pathway, a long-term motor deficit is not indicative of a definitive paresis. Surgery has the potential to release tumor compression to the motor areas with restoration of the normal function. Identification of potential indicators of motor recovery after surgery are of major significance for surgical planning. Here, two possible predictors were identified: 1) Preoperative DTI tractography is a powerful tool to evaluate tract integrity. Reconstruction of the corticospinal tract is indicative of anatomo-functional integrity, despite tract deviation and infiltration. The preoperative depiction of the direction of tract displacement is important for adaptation of the surgical corridor to avoid destruction of the bundles. 2) Intraoperative identification of motor response by electro stimulation confirms the presence of an intact peritumoral tract. Thus, if motor responses are elicited at the primary motor area the resection should stop at this boundary even in cases of long lasting preoperative hemiplegia.

Recent publications had reported high rates of language and memory deficits in GIIG before treatment, with deterioration of the quality of life. We raise the question
if surgery has also the potential to improve these complex cognitive functions. Future studies using a larger number of subjects may bear insight in this interesting issue.

**Disclosure**

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


Figure 1. Case 1. A) Magnetic resonance imaging (MRI) with diffusion tensor imaging (DTI) tractography performed in 2008, when the patient had a normal neurological examination. At this time the left pyramidal pathway had a normal anatomical location, orientation and anisotropy when compared to the contralateral side. B) MRI with DTI tractography performed in September 2009, when the patient had a right hemiplegia. At this time the left pyramidal pathway was deviated posteriorly by the enlarged tumor mass. C) MRI with DTI tractography performed in June 2010, when the patient had improved motor function in the right upper and lower limb. The patient was able to walk independently with a cane and a brace in the right leg. At this time the left pyramidal pathway had recovered the normal position and improved anisotropy.
Figure 2. Case 1. A) Preoperative functional magnetic resonance imaging (fMRI) obtained during imaginary movement of the right hand, demonstrating activity predominantly located in the right precentral gyrus. B) Postoperative fMRI obtained during movement of the right hand, demonstrating activity predominantly located in the right precentral gyrus. C) Preoperative sagittal T1-weighted MRI with diffusion tensor imaging (DTI) tractography reconstruction of the tracts related to motor function: subcallosal fasciculus (1), frontal aslant tract (2), cingulum (3), and corpus callosum(4). Tumor (T). D) Postoperative sagittal T1-weighted MRI with DTI tractography reconstruction of the tracts related to motor function: subcallosal fasciculus (1), frontal aslant tract (2), cingulum (3), and corpus callosum(4). Tumor (T). E) Intraoperative photograph taken before tumor resection showing the tumor margins identified with neuronavigation and marked with a yellow line. The following responses were elicited: red label with number 1 = motor response in the right upper limb; flags = language responses. F) Intraoperative photograph taken after tumor resection. The functional motor and language areas identified have been preserved.

Figure 3. Case 2. A) Magnetic resonance imaging (MRI) with diffusion tensor imaging (DTI) tractography performed in 2007, when the patient had a normal neurological examination. At this time the left pyramidal pathway had a normal anatomical location, orientation and anisotropy when compared to the contralateral side. B) MRI with DTI tractography performed in April 2011, when the patient had a moderate paresis (2/5) of the right foot. At this time the left pyramidal pathway was deviated posteriorly by the enlarged tumor mass. C) MRI with DTI tractography performed in September 2012, when the patient was completely recovered from the right foot paresis. At this time the left pyramidal pathway had recovered the normal position and anisotropy.
Figure 4. Case 2. A) Preoperative functional magnetic resonance imaging (fMRI) obtained during movement of the right leg, demonstrating activity predominantly located in the left precentral gyrus. B) Postoperative fMRI obtained during movement of the right leg, demonstrating activity predominantly located in the left precentral gyrus at the mesial frontal lobe and at the contralateral supplementary motor area. C) Preoperative sagittal T1-weighted MRI with diffusion tensor imaging (DTI) tractography reconstruction of the tracts related to motor function: subcallosal fasciculus (1), frontal aslant tract (2), cingulum (3), and corpus callosum(4). Tumor (T). D) Postoperative sagittal T1-weighted MRI with DTI tractography reconstruction of the tracts related to motor function: subcallosal fasciculus (1), frontal aslant tract (2), cingulum (3), and corpus callosum (4). Tumor (T). E) Intraoperative photograph taken before tumor resection showing the tumor margins identified with neuronavigation and marked with a yellow line. The following responses were elicited: red labels = motor responses in the right upper limb and face; blue labels = sensory responses in the right upper limb; flag = speech arrest. F) Intraoperative photograph taken after tumor resection. The functional motor and language areas identified have been preserved. Direct stimulation at the subcortical level induced motor movement of the right arm and leg (marked with red labels).