

# The preoperative use of navigated transcranial magnetic stimulation facilitates early resection of suspected low-grade gliomas in the motor cortex

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## Abstract

**Background** Resection is recommended for low-grade gliomas, but often it is not performed if the tumor is suspected of invading the primary motor cortex. The study aim is to assess what influence preoperative navigated transcranial magnetic stimulation (nTMS) has on the treatment strategy and clinical outcome for suspected low-grade gliomas in presumed motor eloquent location.

**Methods** This paper reports on all our patients with gliomas in the primary motor cortex that were non-enhancing on MRI, since we began using nTMS (n=11). For the comparison group, we identified the 11 most recent such patients just before we started using nTMS.

**Results** Exact delineation of motor functional versus non-functional cortical tissue was provided by nTMS in all cases, also within the area of altered FLAIR signal. In 6 out of 11 cases, the nTMS mapping result changed the treatment plan towards early and more extensive resection. Only one nTMS patient had another seizure within the follow-up period, whereas four patients in the comparison group had further seizures. In the nTMS group, 1 of 4 patients with pre-op neurological deficits improved by one year; whereas the comparison group had increased neurological deficits in 3 of the 8 patients not having surgery. The median (range) change of tumor volume from baseline to 1 year was -83 % (-67 %

to -100 %) in the nTMS group, but +12 % (+40 % to -56 %) in the comparison group (p<0.001).

**Conclusions** nTMS provides accurate motor mapping results also in infiltrative gliomas and enables more frequent and more extensive surgical resection of non-enhancing gliomas in or near the primary motor cortex. The substantial differences observed here in neurological and oncological outcomes suggest that further comparative research is warranted.

**Keywords** Low-grade gliomas · Motor cortex · Navigated transcranial magnetic stimulation · Neuro-oncology · Surgical resection

## Introduction

Gliomas are brain tumors originating from glia, the supporting cells of the central nervous system and WHO grades them I-IV, according to increasing malignancy [13, 20]. Low-grade gliomas were until recently viewed as benign because patients could live with them for years, so they were “treated” with a wait-and-watch approach [2, 9, 27]. Now, however, grade II gliomas are also viewed as malignant, because inevitably they will become anaplastic and kill the patient [3, 21]. Early resection has been shown to increase survival time over waiting-and-watching [11]. So the recommended first-line treatment for grade II gliomas is undelayed aggressive resection, when possible [1, 11, 25, 31].

Yet, surgical resection can cause motor deficits when gliomas occur in or near the primary motor cortex, and although leading experts and guidelines still recommend resection in such cases [4, 7, 10, 31], many neurosurgeons feel the risk is too high for non-enhancing gliomas and prefer the traditional wait-and-watch approach or non-surgical treatment in such cases [26, 33, 34]. A recent nationwide survey of German academic neurosurgery departments reported that 50 % of all

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**Table 1** Comparison of nTMS case group and historical control group on patient and tumor characteristics

	nTMS Cases	Historical Controls
Sex (n male)	8	6
Age (median)	38	43
Age (range)	20-59	31-71
Tumor side (n left)	3	6
Tumor volume (median, cm <sup>3</sup> )	24	17
Tumor volume (range, cm <sup>3</sup> )	4-105	5-57
Tumor grade (n Grade II)	7	7-10 *
Pre-op MS (n BMRC=5)	9	9
Seizure history (n)	6	9

\* Tumor grade is not known with certainty in all controls. See text

respondents routinely practice a wait-and-watch approach for low-grade gliomas in general [30].

Navigated transcranial magnetic stimulation (nTMS) can be used to map the motor cortex preoperatively [23]. The aim of this report is to assess the difference in treatment strategy for non-enhancing gliomas in or near the motor cortex when the patient receives nTMS mapping.

**Methods**

**Study design and sample**

The study is designed as an observational comparative effectiveness study. The prospective nTMS group includes all patients with non-enhancing gliomas suspected of invading the primary motor cortex, seen at our department since we began using nTMS in October 2007 through the

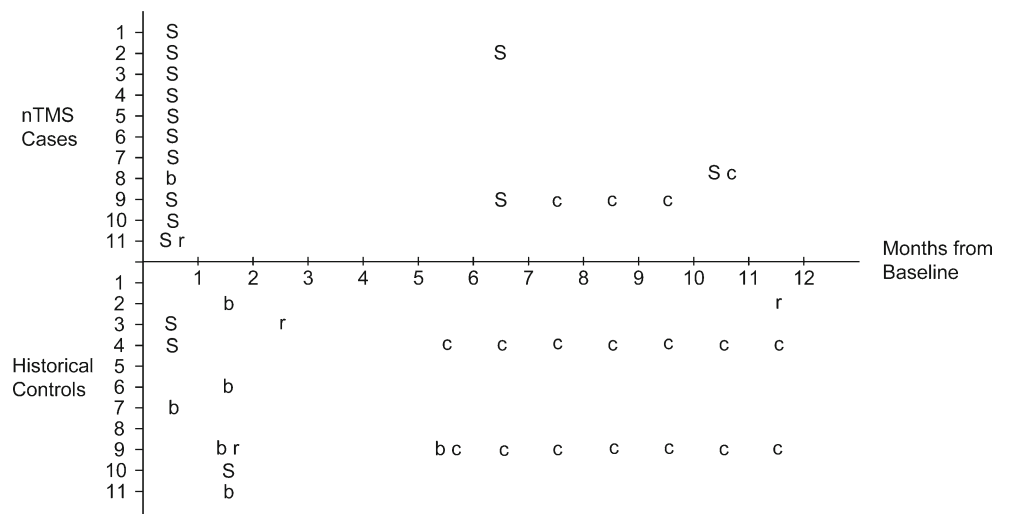
**Fig. 2** Imaging and key information on the nTMS cases. The figure shows the pre-op MRI, the pre-op TMS map, and the post-op MRI for all 11 nTMS cases. Each row of text and figures is for one patient. The text in each row presents the case number, sex, and age of the patient; the hemisphere, location, and volume of the tumor; and the extent of surgical resection achieved. The left column of figures is the pre-op MRI. The central column of figures is the TMS map. Colored pins indicate points where TMS resulted in a motor response; gray pins indicate points where TMS did not result in a motor response. We have outlined the MRI T1 area (solid tumor) in red and MRI FLAIR area (tumor invasion) in yellow. The right column of figures is the post-op MRI which is a matching slice to the pre-op image. Pre-op and post-op MRIS are without contrast enhancement. Two cases (#2, 9) had a second surgery at 7 months using a new nTMS mapping (images not shown). On the cortical level, the DES “stop signal” always coincided with the resection margins determined preoperatively with nTMS

end of 2010 (n=11). To form a comparison group, we performed a post hoc analysis of prospectively collected data of our last 11 patients before we introduced nTMS who had non-enhancing gliomas suspected of invading the primary motor cortex (September 2001 to April 2007). To facilitate comparison, we limit ourselves to the first year from the initial presentation. Collection of data was approved by the university hospital’s ethics commission (reference # EA4/007/06).

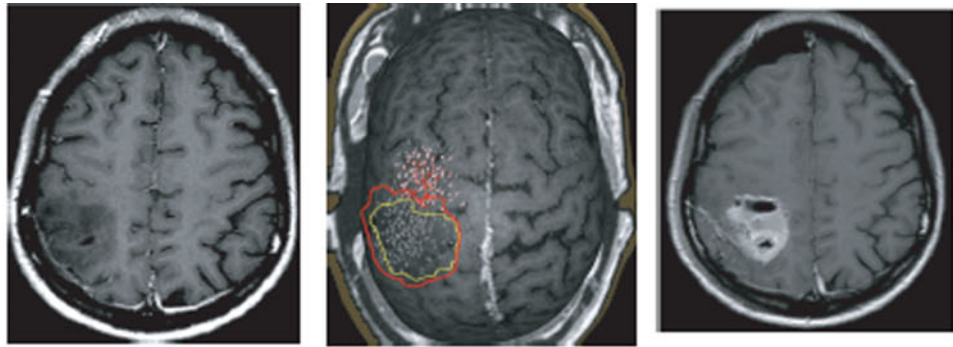
**Preoperative diagnostics**

All patients underwent brain mapping with nTMS (eXimia; Nexstim; Helsinki, Finland), as described previously [23]. Briefly, magnetic stimulation was applied transcranially to points of the brain in and around the tumor, and the motor response was recorded by EMG. This enabled us to map the cortical areas essential for motor function.

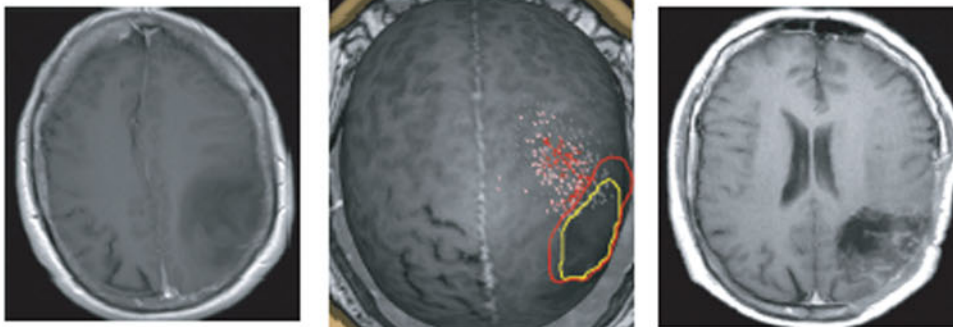
**Fig. 1** Course of treatment. The x-axis show the time from initial presentation; yhe y-axis shows the subject numbers. S surgery, b biopsy, r radiotherapy, c chemotherapy. The timeline is only accurate to the nearest month, but the sequence of letters does properly indicate the sequence of treatments when more than one occurred in the same month



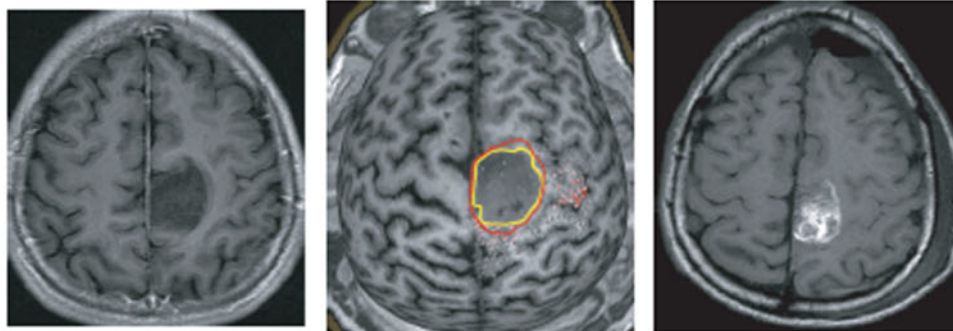
#1: F 33  
L postcentral  
28 cm<sup>3</sup>  
T1 + part FLAIR



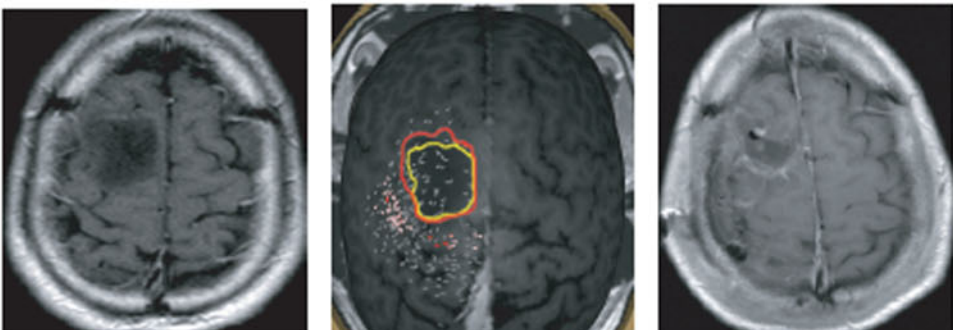
#2: M 44  
R postcentral  
105 cm<sup>3</sup>  
T1 + part FLAIR



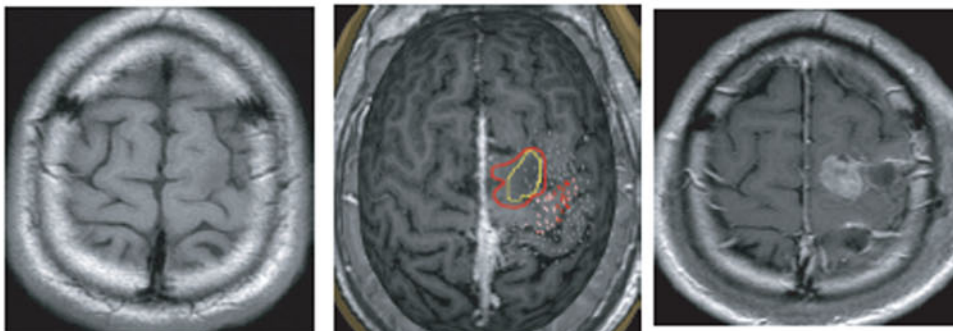
#3: M 20  
R precentral  
30 cm<sup>3</sup>  
total tumor



#4: M 38  
L precentral  
18 cm<sup>3</sup>  
total tumor



#5: M 24  
R precentral  
6 cm<sup>3</sup>  
T1 + all FLAIR



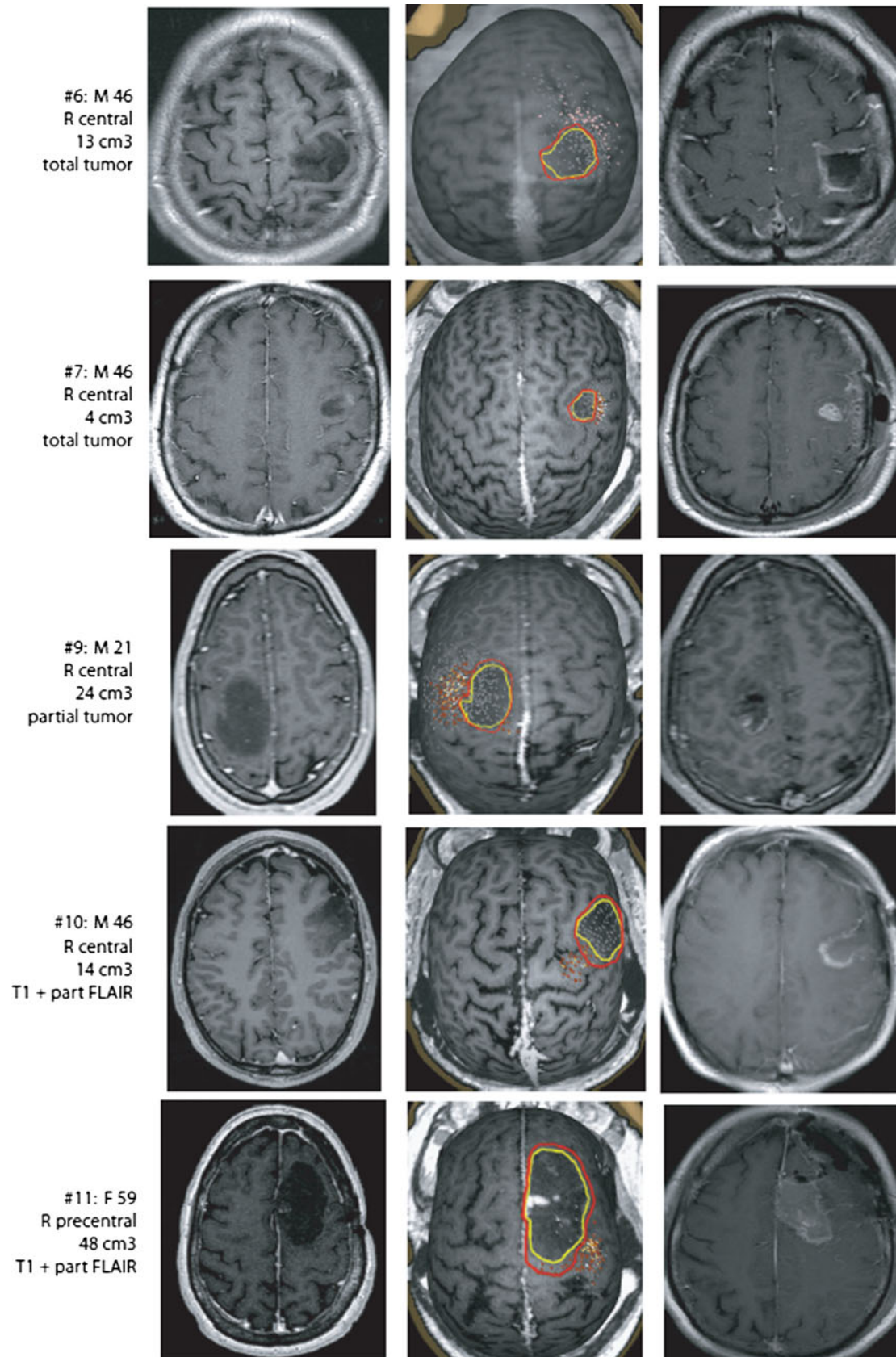
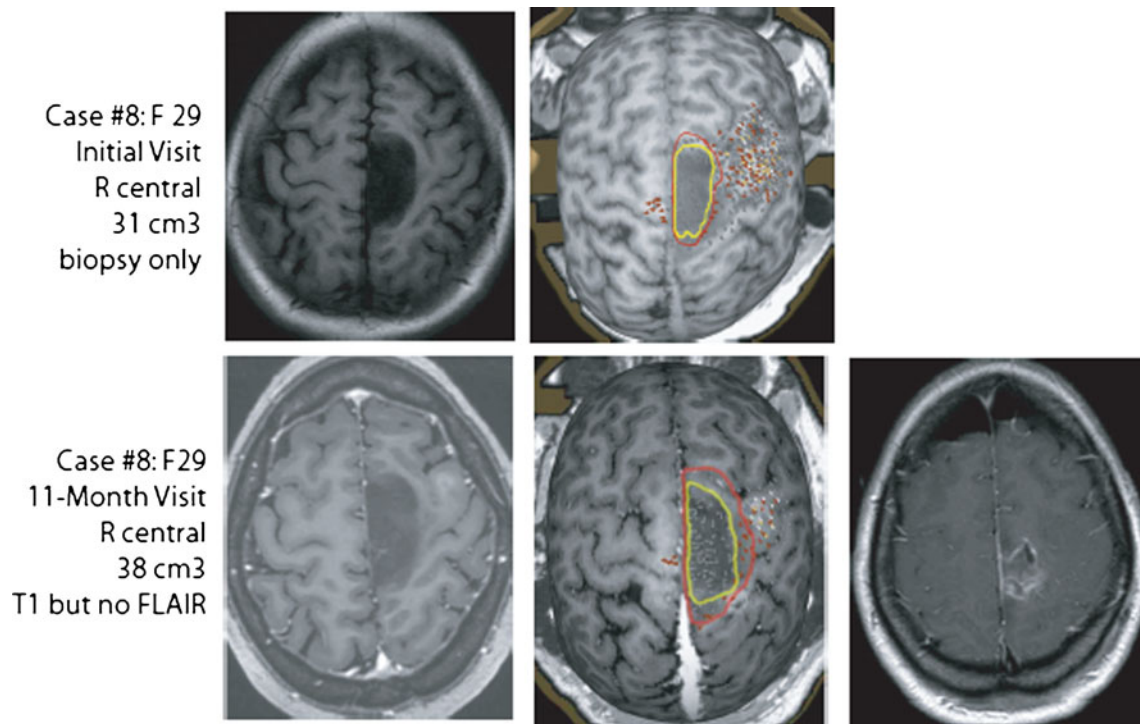


Fig. 2 (continued)



**Fig. 2** (continued)

#### Influence on surgical planning

The nTMS results were presented to the surgeon only after the treatment strategy had been stated based on the anatomical MRI's alone. The surgeon then revised the surgical plan if desired and evaluated the influence of the nTMS results on the surgical planning, using a 0–6 descriptive categorical ranking questionnaire, as previously described [24].

#### Surgery

Surgery was performed in a standard fashion under general anesthesia, using neuronavigation, somatosensory electric potential phase reversal, and direct electrical stimulation (DES), as described previously in greater detail [23, 32]. The nTMS mapping result was confirmed by DES in all cases.

#### Clinical data

Motor status was graded on the BMRC scale (British Medical Research Council scale for muscular strength). The tumor location was determined by the Department of Radiology on the basis of MRI. Tumor volume was measured from the FLAIR-weighted MRIs. Tumor histology was determined post-operatively by the Department of Pathology on the basis of resected tissue samples.

#### Results

##### Study sample

The two study groups were quite similar (Table 1). Based on anatomical MRI, all tumors were suspected of invading the precentral gyrus. All tumors had well defined brain–tumor interfaces with the FLAIR signal abnormality only slightly exceeding the T1 hyperintense area.

##### Treatment course

The treatment course during the first year is presented in Fig. 1. Nearly all nTMS patients had surgery within the first month. Only three historical patients (# 3, 4, 10) received surgery during the first year. Chemotherapy was not used more in the historical group than the nTMS group (n=2 in each group), and radiotherapy was also not used strikingly more in the historical group (n=3 during 1 month each) than in the nTMS group (n=1 during one month). Three patients in the historical group (# 1, 5, 8) never received any form of oncological treatment at all during the first year.

##### Navigated transcranial magnetic stimulation (nTMS)

The MRIs and nTMS mapping are shown in Fig. 2. nTMS demonstrated that there was no motor function within the solid tumor mass (the T1 hypointense area) in any case

(Fig. 2 – middle column). In six cases (# 1, 2, 5, 8, 10, 11), the MRI FLAIR area was slightly larger than the T1 hypointense area, and nTMS identified motor function within this excess FLAIR area in all 5 cases where it was performed.

#### Influence on surgical planning

The addition of the nTMS data changed the surgeon's approach in four cases (36 %) towards a more extensive resection (cases #3, #4, #5, #11) and in two cases (18 %) the surgical indication was changed (cases #3, #6)—meaning that without the nTMS data, the surgeons would have opted for watchful waiting, which is not uncommon if the tumor is predominantly located within an area which normally carries essential function [12, 30].

#### Surgery

The solid tumor mass was completely resected in 10 of 11 nTMS cases (Fig. 2, right column). In the six cases where the MRI FLAIR area noticeably exceeded the T1 hypointense area (# 1, 2, 5, 8, 10, 11), the resection usually extended beyond the solid tumor mass into this presumed tumor infiltration zone, except where nTMS and DES had confirmed function. Three historical controls (#3, 4, 10) had surgery, but only a partial resection was achieved: about 5 % of T1 in control #3, 70 % in control #4, and 60 % in control #10.

#### Pathology

All cases and controls were initially believed to have low-grade gliomas, because of the lack of contrast enhancement on MRI, and this was confirmed histologically in the majority of patients in each group (Table 1). However, 4 of 10 nTMS cases with early surgery and 1 of the 3 controls who had surgery were determined to already have grade III gliomas, despite the lack of contrast enhancement. The nTMS case who first had surgery at 11 months was also grade III by that time, despite an early biopsy reporting grade II. Three historical controls had no laboratory assessment at all within the first year (Table 1).

#### Motor outcomes

In each group, 10 of 11 patients had the same motor status one year after the initial presentation as they did initially. The remaining nTMS patient (#6) reported at one-year follow-up a slight loss of occupationally necessary fine motor skills (BMRC 5), and the remaining historical control (#10) had BMRC 4 due to surgery.

#### Other neurological outcomes

Only 1 of 6 nTMS patients with a seizure history had further seizures (the patient who had delayed surgery); whereas, 6 of 9 controls with a seizure history had further seizures (Table 2). The proportion of patients with other neurological deficits was initially similar in the two groups but had better outcomes in the nTMS group (Table 2). Surgery in the nTMS group led to no patient becoming worse (according to BMRC grading) and 1 of 4 patients with pre-operative deficits having an improvement. By contrast, 5 of the 8 historical controls without surgery had increased neurological deficits, while there was no change in the 3 controls with partial resections.

Postop refers to the first year from the initial visit. Y yes, dash none, FMS fine motor skills, BMRC British Medical Research Council scale for muscular strength, R right, L left

#### Oncological outcomes

The median (range) change of tumor volume from baseline to 1 year for the 11 nTMS cases was –83 % (–67 % to –100 %). By contrast, the median (range) change of tumor volume at 1 year for the 11 controls was +12 % (+40 % to –56 %). Despite the small sample size, this difference between the two groups (Fig. 3) was so substantial that it was also statistically highly significant ( $p < 0.001$  by Mann Whitney rank sum). Additionally, one control had progressed from grade II to grade III, while none of the nTMS patients had progressed.

#### Discussion

Although low-grade gliomas are not “aggressive” (i.e., fast-growing and fast-spreading), they are “malignant”, because inevitably they will become anaplastic and kill the patient. In the meanwhile, their presence in the patient's brain can cause epileptic seizures, deterioration of motor function, and other neurological deficits. For these reasons, it is now widely recognized that low-grade gliomas should be surgically resected [1, 11, 25, 31], especially since some non-enhancing gliomas may already be high-grade [8, 18, 21, 26, 29]. Yet research has documented that 50 % of neurosurgeons do not operate on non-enhancing gliomas in general [30], and the rate could be worse when the tumor occurs in the primary motor cortex where resection can cause permanent functional deficits [12]. Here we have shown that nTMS can help to adopt the state-of-the art treatment strategy, i.e., early and aggressive resection of LGGs guided by DES, by proving – preoperatively – which cortical areas are functionally essential.

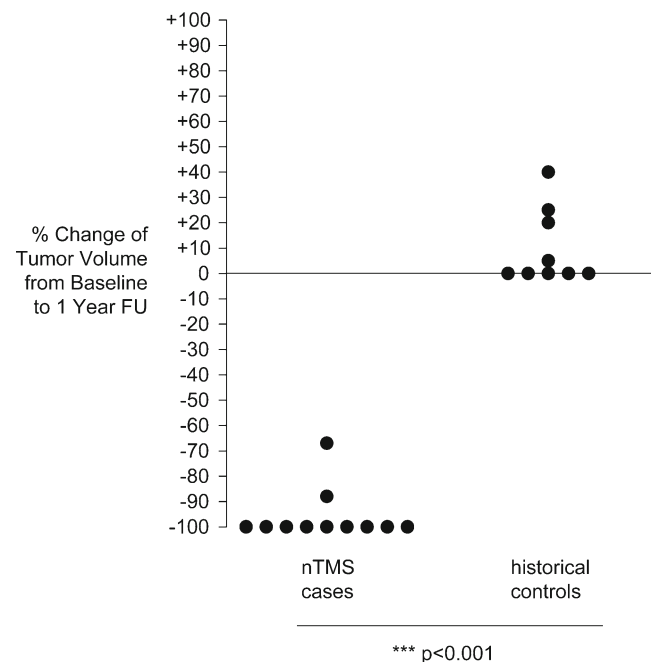
Several main lessons can be drawn from this study. First, without preoperative nTMS mapping, surgeons in this series have been hesitant to resect a non-enhancing glioma suspected

**Table 2** Neurological deficits

#	Seizures		Motor Deficit		Other neurological deficits	
	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.
<u>nTMS Cases</u>						
1	-	-	-	-	weak concentration, depressive disposition	concentration and disposition improved
2	Y	-	Y	unchanged	headache	unchanged
3	-	-	-	-	-	-
4	-	-	Y	unchanged	-	-
5	-	-	-	-	-	-
6	Y	-	-	reduced FMS	L arm pain	unchanged
7	-	-	-	-	-	-
8	Y	Y	-	-	weak concentration	unchanged
9	Y	-	-	-	-	-
10	Y	-	-	-	-	-
11	Y	-	-	-	-	-
<u>Historical controls</u>						
1	Y	-	-	-	-	-
2	Y	Y	-	-	-	headache, dizziness
3	Y	Y	-	-	-	-
4	Y	Y	-	-	-	-
5	Y	-	Y	unchanged	slight aphasia	slight aphasia progressed, dizziness
6	Y	Y	-	-	-	-
7	-	-	-	-	headache, tiredness	unchanged
8	-	Y	-	-	-	-
9	Y	Y	Y	unchanged	neuropsychological changes	neuropsychological changes stable, slight aphasia, headache, nausea, dizziness
10	Y	-	-	BMRC 4	-	-
11	Y	-	-	-	-	-

of invading the primary motor cortex. Consequently, the patient's tumor will grow, and their neurological status will deteriorate. Second, nTMS allows to delineate motor functional from non-functional cortical tissue even within the area of altered FLAIR signal. Third, although the resection should still be guided by intraoperative DES [5, 6], preoperative nTMS functional mapping is what provides the necessary pre-operative guidance, reassurance, and planning [24], that enables neurosurgeons to make the decision to schedule a patient with a LGG within the primary motor cortex for surgery. In this series, the strategy was changed from watchful waiting to resection in two cases after the nTMS mapping results were added to the risk-benefit balancing.

DES was always available here and could have been used, but without preoperative nTMS, surgeons at our department often never even attempted surgery, and when they did, resection was never complete because they were reluctant to aggressively resect to the functional borders, even though the gold standard of DES was being performed by a highly experienced team [14–17, 22]. Fourth, surgical resection can lead to immediate improvements in the patient's neurological

**Fig. 3** Change of tumor volume. Each dot represents one patient

health and usually succeeds at eliminating the entire solid tumor mass, which should improve their life-expectancy [11, 28, 31]. Any remaining risk of motor deficits or other complications from surgery are outweighed by the neurological and oncological risks of not resecting the glioma.

Our study is limited by its use of a retrospective comparison group from previous years. The outcome differences we observed could be due in part to other factors that changed over the years, especially the increased awareness of the need for prompt surgery. Nonetheless, the functional nTMS cartography with the exact delineation of resectable versus non-resectable cortical tissue, even within the area of altered FLAIR signal, had a significant effect on treatment decisions leading to earlier and more extensive resections. This confirms previous observations about the impact of nTMS on the surgical strategy [19, 24]. Further carefully designed clinical trials and multicenter patient registries are now warranted to double-verify how much of the treatment effect observed here is truly attributable to the preoperative use of nTMS.

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## Comment

Picht et al. present a study where they assessed the usefulness of preoperative navigated transcranial magnetic stimulation for the surgery of presumed low grade astrocytomas. This topic is interesting as nTMS is a relatively new tool, is not part of the standard armamentarium of most neurosurgical centers and therefore its use is limited and its usefulness still uncertain.

The goal of the study is to define the impact of this technology on the surgical results and on the overall clinical course of patients with

presumed WHOII gliomas in or invading the motor cortex. The authors describe their experience with 11 patients and show convincingly good results in terms of extent of resection and low postoperative deficits. Every neurosurgeon knows from experience that lesions in the primary motor cortex are challenging and prone to postoperative motor deficits. Therefore we can appreciate the good results shown by the authors and reasonably deduct that nTMS probably provided an advantage, be it solely the confidence to offer surgery and attempt an extensive resection.

The comparison with an historical group can be useful for the assessment of new technology that is not easily subjected to randomized control trials and the number of patients is low. However, this requires homogenous groups which is not the case here and this is the main flaw of this study. Scientifically, the historical groups are not comparable. The study assesses what the availability of TMS changes in the overall management of these patients. However, this study does not compare surgery with or without TMS nor does it provide comparative data on observation vs Surgery (with or without TMS). Therefore any conclusion about the safety of surgery or the specific contribution of TMS to surgical outcomes cannot be drawn. Furthermore heterogeneity between groups is introduced by the fact that there were grade II and III tumors in both groups but some historical cases do not have a definitive diagnosis.

After all it could well be that surgery with DES alone is equal to nTMS and that the number of patients undergoing surgery in the nTMS group are the result of a change in the surgical philosophy for these lesions overtime.

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