



Case Report

# Integrating navigated transcranial magnetic stimulation motor mapping in hypofractionated and single-dose gamma knife radiosurgery: A two-patient case series and a review of literature

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## ABSTRACT

**Background:** The aim of the study was to demonstrate the feasibility of integrating navigated transcranial magnetic stimulation (nTMS) in preoperative gamma knife radiosurgery (GKRS) planning of motor eloquent brain tumors.

**Case Description:** The first case was a 53-year-old female patient with metastatic breast cancer who developed focal epileptic seizures and weakness of the left hand. The magnetic resonance imaging (MRI) scan demonstrated a 30 mm metastasis neighboring the right precentral gyrus and central sulcus. The lesion was treated with adaptive hypofractionated GKRS following preoperative nTMS-based motor mapping. Subsequent follow-up imaging (up to 12 months) revealed next to complete tumor ablation without toxicity. The second case involved a previously healthy 73-year-old male who similarly developed new left-handed weakness. A subsequent MRI demonstrated a 26 mm metastatic lesion, located in the right postcentral gyrus and 5 mm from the hand motor area. The extracranial screening revealed a likely primary lung adenocarcinoma. The patient underwent preoperative nTMS motor mapping prior to treatment. Perilesional edema was noted 6 months postradiosurgery; nevertheless, long-term tumor control was demonstrated. Both patients experienced motor function normalization shortly after treatment, continuing to final follow-up.

**Conclusion:** Integrating preoperative nTMS motor mapping in treatment planning allowed us to reduce dose distributions to perilesional motor fibers while achieving salvage of motor function, lasting seizure freedom, and tumor control. These initial data along with our review of the available literature suggest that nTMS can be of significant assistance in brain radiosurgery. Prospective studies including larger number of patients are still warranted.

**Keywords:** Adaptive hypofractionated gamma knife radiosurgery, Karnofsky performance scale, Magnetic resonance imaging, Motor region, Single-dose gamma knife radiosurgery, Transcranial magnetic stimulation

## INTRODUCTION

The surgical management of metastatic lesions in the eloquent brain remains complex in terms of tumor control and preservation of neurologic function, particularly in cortical motor areas

where functional relevance is difficult to predict purely from anatomical imaging studies. The application of presurgical functional mapping with the aim of modifying microsurgery planning and reduce postoperative functional deficits is now a common procedure; the unique meta-analysis by Raffa *et al.* provides further support to the latter concept and remains to date an unequivocal landmark of reference.<sup>[1,3-6,11-13,16,20,24-26,31,37-39,44,53,54,55,58]</sup> In this surgical context, navigated transcranial magnetic stimulation (nTMS) is a well-established, noninvasive, painless electromagnetic pulse-based procedure known to stimulate cortical neurons just beneath the coil;<sup>[2]</sup> when magnetic resonance imaging (MRI) guided,<sup>[43]</sup> nTMS can be successfully utilized to accurately identify the cortical motor and speech areas before microsurgery. However, the role of nTMS in stereotactic radiosurgery has not been equally explored.<sup>[6,20,38]</sup> Gamma knife radiosurgery (GKRS) is a radiosurgical modality used in the upfront or complementary surgical management of brain metastases.<sup>[23,33,35,49]</sup> Although tumor control rates remain high, the development of adverse radiation effects (AREs) in eloquent brain remains a concern, particularly in the presence of large tumor volume and/or radioresistant histologies.<sup>[29,32,48]</sup> In these cases, the design of GKRS-treatment plans optimizing ablative dose distributions within tumor boundaries while limiting toxic dose dissipation to functional cortical/subcortical areas is of utmost importance. We present our institutional experience integrating preoperative nTMS motor mapping in the context of two separate GKRS treatment modalities, involving two adult patients (one treated with adaptive hypofractionated GKRS and the other with single fraction GKRS). The primary objectives of this study were to check the feasibility of nTMS data transfer to the Leksell GammaPlan® (LGP) system and to observe the potential impact of nTMS on GKRS treatment planning in terms of (i) dose dissipation in mapped functional areas, (ii) achievement of tumor reduction/ablation, (iii) development of AREs, and (iv) post-GKRS motor functional outcome. To confirm possible GKRS associated functional deficits, key data were obtained comparing post-GKRS nTMS motor mapping to pre-GKRS functional estimates. To the best of our knowledge, this is the first feasibility study integrating nTMS to GKRS planning in Scandinavia.

## MATERIALS AND METHODS

### Inclusion criteria

Subject to multidisciplinary discussion, as well as institutional and ethical approval, two adult patients with MRI-verified metastatic lesions in or adjacent to cortical motor areas were recruited for the purpose of this study. In both cases, microsurgery was deemed less suitable than radiosurgery due to topoanatomical limitations and the

extension of extracranial metastatic disease; other forms of radiotherapy or systemic treatment were assessed as of no benefit to these patients. Patients were required to have a Karnofsky Performance scale (KPS) of at least 70 (recursive partitioning analysis [RPA] 1–2). Previous microsurgery, presence of perilesional edema (resistant to steroids or not) and extracranial tumor activity were not criteria for exclusion. However, future or ongoing oncological treatment and survival expectancy of at least 6 months were mandatory. In this particular setting, one patient was accepted for dose-volume adaptive hypofractionated GKRS while the other was planned for single-dose GKRS.

### Pre- and post-GKRS nTMS protocol

Protocols for nTMS motor mapping followed updated institutional guidelines and previously published medical data.<sup>[26]</sup> In each case, muscles were chosen in accordance with the lesion's specific location (Table 1 for details of chosen muscles). The eXimia NBS system 4.3 (Nexstim, Helsinki, Finland) equipped with a stereotactic navigation system and a 6-channel electromyography (EMG) recorder was used. Single-pulse TMS was delivered with a focal biphasic figure-of-eight coil (70 mm outer diameter; Nexstim Ltd., Helsinki, Finland) affecting an area of about 1.7 cm<sup>2</sup> or smaller.<sup>[45]</sup> Motor evoked potential (MEP) data from the eXimia system (sampling rate 3000 Hz) were obtained, using the surface EMG electrodes (Neuroline 715, Ambu, Ballerup, Denmark), attached to muscles contralateral to the stimulated hemisphere. Subject-specific MRI was used to reconstruct the head model. Structural MRI of the brain, with a suitable navigation sequence (axial 3D BRAVO 1 mm reformatted in three planes, FoV 256 mm, NEX 1, TR 8.16, TE 3.18, TI 450, Flip angle 12, 1.5 T, GE Discovery 450 CE) was acquired earlier. During the TMS session, the patient's head was first coregistered with the corresponding MRI; then, the standard tracking unit was fixed to the patient's forehead allowing real-time navigation.<sup>[43]</sup> Initially, the resting motor threshold (rMT) was estimated and used as a marker for subject-specific cortical excitability. All relevant rMT-estimations were measured for both hemispheres. Motor mapping was done at 110% of rMT.

### Complementary studies: pre- and post-GKRS electroencephalography (EEG)

Both patients were examined pre- and posttreatment with complementary scalp-EEG studies. Electrodes (21-scalp electrodes) were positioned using the 10–20 system; Fp1, Fp2, F7, F8, T3, T4, T5, T6, O1, O2, F3, F4, C3, C4, P3, P4, Fz, Cz, Pz, A1, and A2. Electrode impedances were kept below 5 kΩ. The recording consisted of 30 min of spontaneous activity with the patient awake in a supine position. The patients were provoked using 3 min of hyperventilation and

**Table 1:** nTMS data for both cases.

	rMT (%) of MSO		Muscles				
			Preoperative		12 months follow-up		
	Right hemisphere	Left hemisphere	Amp ( $\mu$ V)	Lat (ms)	Amp ( $\mu$ V)	Lat (ms)	
Case 1							
Pre (November, 2016)	40	25	APB <sup>dx</sup>	157	23.1	221	23.3
Post (May, 2017)	38	24	FDI <sup>dx</sup>	314	23.3	206	23.3
			EDC <sup>dx</sup>	51	20.2	67	19.3
Case 2							
Pre (October, 2016)	28	28	APB <sup>sin</sup>	672	28.6	281	24.3
Post (April, 2017)	22	22	FDI <sup>sin</sup>	1885	26.8	251	23.9
			EDC <sup>sin</sup>	1370	20.7	325	20.4
			AH <sup>sin</sup>	979	49.9	134	49

rMT: Resting motor threshold, MSO: Maximum stimulator output, APB: Abductor pollicis brevis, FDI: First dorsal interossei, EDC: Extensor digitorum communis, AH: Abductor hallucis

photostimulation. The pre- and posttreatment EEGs showed no epileptiform activity; however, in Case 2, a focal slowing was demonstrated before and after the radiosurgery in the right central regions.

### Integrating nTMS motor assessments to GKRS planning

Optimal cranium fixation was achieved mounting the stereotactic Leksell® frame. As a result, no margins were required outside the gross tumor volume limits. To attain ideal dynamic target definition, a stereotactic MRI was performed before each GKRS. MRI sequences included pre- and postgadolinium enhanced T1 fast spin echo, postgadolinium 3D T1-weighted volume FSPGR reconstructed in three planes as well as axial T2-weighted propeller, 1.5 T GE Discovery 450w. All positive nTMS points were fused together with the anatomical MRI obtaining identifiable motor points deemed as organs at risk (OAR) ultimately saved as a digital imaging and communication file. The data were then successfully imported to the LGP system and taken into consideration for GKRS planning. The corresponding GKRS treatment plan was set on the preoperative MRI evolution, and the presence of treatment feasibility variables described elsewhere.<sup>[17,22]</sup> For Case 1, we designed a regimen of three GKRS-interventions during the course of 7 days to adapt radiation doses to expected morphological changes during the course of treatment. Each fraction was to be delivered every 72 h. Further setup characteristics have been explained in prior reports.<sup>[17,22]</sup> For Case 2, single-dose GKRS-treatment was designed to deliver a peripheral dose of at least 18 Gy at the 50% isodose line due to its relatively smaller volume. To monitor possible radiation-induced plastic changes while adapting to extracranial disease evolution, a follow-up (second) nTMS was to be performed at least 6 months, but no more than 12 months, post treatment on both patients (see discussion).

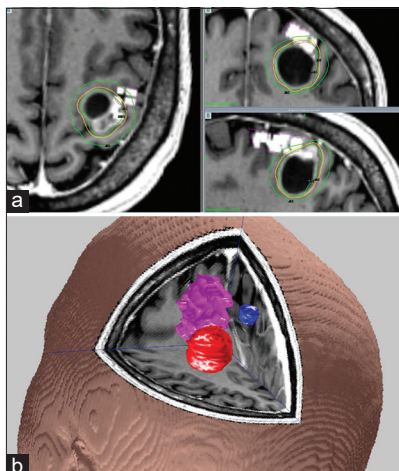
### Case description

#### Case 1

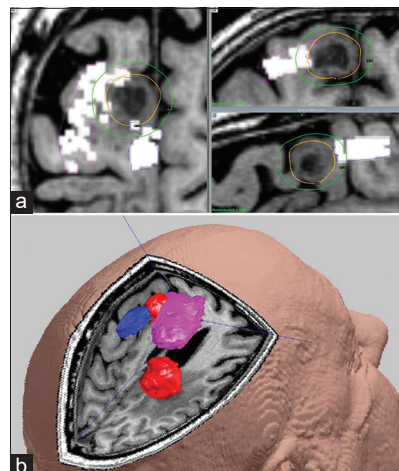
A 53-year-old female patient with metastatic breast cancer, previously treated with both chemo- and immunotherapy, developed focal epileptic seizures involving her right arm. The investigative computed tomography (CT)-scan and MRI of the brain showed four intra-axial metastases, the largest (6.7 cc) located in the left precentral gyrus (M4). Extracranial CT screening showed stable appearances of disease, including her liver metastases. The patient was planned for adaptive hypofractionated GKRS of M4 and for single fraction GKRS treatment for the remaining lesions (M1-M3); due to their “safe” location, M1-M3 were excluded from this study. A preoperative nTMS for perilesional motor-mapping was performed the day before GKRS 1 (November 2016). In this case, a total of three muscles from the upper limb (adjacent to M4) were mapped and identified as OAR [Figure 1 a and b]. rMT was measured for both hemispheres, which showed a clear side differential (left > right); MEP amplitudes and latencies were within normal range [Table 1 for detail neurophysiological values]. At GKRS 1, the patient was still suffering from focal seizures despite antiepileptic treatment (equivalent to Engel-score scale 2–3) but with almost immeasurable right-hand weakness; her KPS was assessed as 100.

#### Case 2

A previously healthy 73-year-old man developed gradual left-hand paresis (September 2016). A brain CT and subsequent MRI showed a 26 mm metastatic lesion in the right postcentral gyrus and postcentral sulcus, 5 mm from the hand motor cortex (M1), as well as an 18 mm metastasis (M2) located medially in the right superior frontal gyrus. Due to its



**Figure 1:** Structural image showing lesion and gamma knife radiosurgery (GKRS) planning in Case 1. (a) Yellow line = peripheral prescription isodose line. Outer and inner green lines = dose distribution inside and outside target. White rectangles = navigated transcranial magnetic stimulation (nTMS) motor points overlaid at 20–25 mm depth. (b) Magnetic resonance-images superimposed with pre-GKRS nTMS-determined organs at risk representing the arm and hand motor function areas for Case 1. Red = gross tumor volume (treatment target); Magenta = upper limb; Blue = lower limb.



**Figure 2:** Structural image showing lesion and GKRS planning in Case 2. (a) Yellow line = peripheral prescription isodose line. Outer green line = dose distribution outside target (10 Gy-isodose line). White rectangles = navigated transcranial magnetic stimulation motor points overlaid at 20–25 mm depth. (b) Magnetic resonance-images superimposed with transcranial magnetic stimulation for Case 2. Gross tumor volumes in red (most anterior target included in the study) and organs at risk in magenta (upper limb) and blue (lower limb).

location, M2 was deemed safe for GKRS and excluded from this study; both lesions had extensive perilesional edema. An investigative CT-scan of the thorax and abdomen revealed a 6 cm lung tumor in the right lower lobe as well as mediastinal lymph node infiltration. The histology of the primary was then confirmed to be a lung adenocarcinoma (October 2016). The patient was accepted for upfront GKRS management of M1 and M2 before starting systemic treatment. As in the first case, the patient underwent a preoperative nTMS for perilesional motor-mapping before starting treatment. Likely secondary to ongoing steroid treatment, the underlying nTMS MRI revealed a slight volume reduction of M1 (24 mm, vol =5 cc) while unchanged volumetry for M2 (1.3 cc). Due to the location of M1 in relation to the motor homunculus, three muscles from the upper limb and one lower limb muscle were mapped and identified as OAR [Figure 2a and b, Tables 2 and 3]. Based on nTMS-based estimates, M1 was treated with a peripheral dose of 20 Gy at the 50% isodose line (one fraction). At GKRS, the patient presented with slight fatigue and a subjective (hardly measurable) left-hand weakness. However, he remained seizure-free (Engel score scale 1) with a KPS of 90.

**RESULTS**

**Case 1**

The treatment was well tolerated. M4 was 7.4 cc at GKRS 1; 16% of volume reduction was achieved between

**Table 2:** Case 2 – Dose distribution outside target to upper and lower limb muscles (=OAR).

	4 Gy volume to OAR	6 Gy volume to OAR	10 Gy volume to OAR
Without integrated nTMS			
Upper limb	2.89	1.53	0.78
Lower limb	0.8	0.49	0.18
With integrated nTMS			
Upper limb	2.29	1.10	0.56
Lower limb	1.1	0.41	0.12

OAR: Organs at risk, nTMS: Navigated transcranial magnetic stimulation

**Table 3:** Case 2 – Total 10 Gy-volume and selectivity estimates (illustrating dose dissipation outside target) and tumor bed coverage with and without integrating nTMS to single-dose GKRS treatment planning (applying a peripheral dose of 20 Gy).

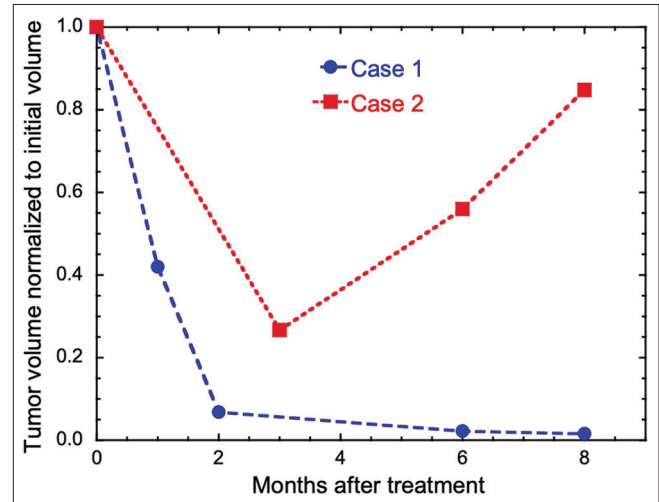
	10 Gy volume (cc)	Selectivity	Tumor coverage (%)
Without nTMS	4.9	0.80	99
With nTMS	3.4	0.85	98

nTMS: Navigated transcranial magnetic stimulation, GKRS: Gamma knife radiosurgery

GKRS 1 and GKRS 3 [Table 4]. The reduction of dose dissipation to the OAR based on nTMS data was around 50% at each fraction without compromising intratumoral dose deployment [Tables 5 and 6]. Motor symptoms and epileptic seizures subsided within weeks after treatment completion. Follow-up MRI at 1 month and subsequent imaging showed considerable tumor volume reduction of M4 compared to GKRS 1 (>95% at 12 months follow-up MRI) without evidence of ARE [Table 7, Figure 3]. The remaining lesions had also responded to treatment. The postsurgical nTMS at 12 months was performed using similar stimulation guidelines, registering from the same muscles. Like the preoperative nTMS, rMT showed a clear side difference (left > right). However, MEP amplitudes and latencies were within normal range [Table 1]. The corresponding representation of the hand motor area at this stage showed no identifiable distortions [Figure 3]. GKRS had neither affected nor distorted the functional configuration mapped on the nTMS examination at pre and post-GKRS, hence successfully managing to preserve/salvage local neurological function. At 12 months follow-up, the patient had ongoing treatment for her extracranial disease (KPS 70). No major neurological deficit, cognitive impairment or epileptic activity was reported at this stage.

**Case 2**

As in Case 1, the treatment was well tolerated. Follow-up MRI at 1 month showed slight volume reduction of M1 and M2 as well as reduced edema. The follow-up CT scan



**Figure 3:** Tumor volume dynamics post-GKRS (see table 8). Case 1: optimal tumor ablation. Case 2: initial tumor volume reduction followed by ARE-evolution.

**Table 4:** Case 1 – Tumor volume dynamics between GKRS 1 and GKRS 3 (above) and corresponding peripheral prescription doses at each GKRS (below).

	GKRS 1	GKRS 2	GKRS 3
Tumor volume	7.40 cc	6.8 cc	6.2 cc
Prescription dose	8.00 Gy at the 35% isodose line	9.00 Gy at the 35% isodose line	9.00 Gy at the 35% isodose line

GKRS: Gamma knife radiosurgery

**Table 5:** Case 1 – Radiation dose dissipation to OAR (three muscle groups of the upper limb) without nTMS and with nTMS at each GKRS. Substantial sparing of healthy tissues was achieved by integrating nTMS.

	4 Gy-isodose volume to the OAR (cc)			6 Gy-isodose volume to the OAR (cc)		
	GKRS 1	GKRS 2	GKRS 3	GKRS 1	GKRS 2	GKRS 3
Without integrated nTMS	1.07	1.43	1.32	0.42	0.68	0.6
With integrated nTMS	0.68	0.54	0.6	0.23	0.26	0.27

OAR: Organs at risk, nTMS: Navigated transcranial magnetic stimulation, GKRS: Gamma knife radiosurgery

**Table 6:** Case 1 – Dose distribution inside the tumor at 10 Gy, 12 Gy, 15 Gy. Dose distributions required to achieve tumor ablation remained nearly unaffected when integrating nTMS in treatment planning.

	10 Gy volume (%)			12 Gy volume (%)			15 Gy volume (%)		
	GKRS 1	GKRS 2	GKRS 3	GKRS 1	GKRS 2	GKRS 3	GKRS 1	GKRS 2	GKRS 3
Without nTMS	80	96	96	60	79	80	32	55	54
With nTMS	80	95	96	57	74	74	30	46	45

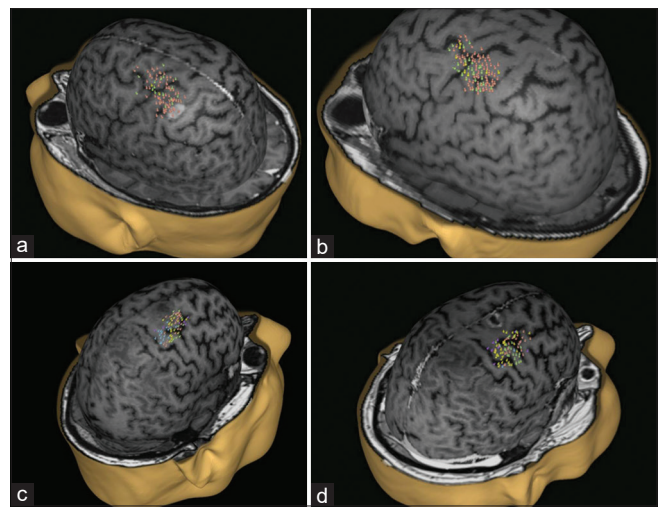
nTMS: Navigated transcranial magnetic stimulation, GKRS: Gamma knife radiosurgery

at 3 months showed further volume reduction of M1 and M2 but progression of the perilesional edema around M1 subsequently assessed as an ARE [Table 8]. At this point, the patient was suffering from intermittent confusion, expressive dysphasia and further weakness of his left hand; the patient's condition improved with steroids shortly thereafter. A complementary MRI 3 weeks later demonstrated a decrease in perilesional edema around M1. Despite an Engel score of 1, the patient started prophylactic antiepileptic treatment at this time. Unlike Case 1, the patient underwent a follow-up nTMS 6 months after treatment completion (April 2017) due to MRI-confirmed ARE-persistence around M1 [Table 8, Figures 3 and 4] and progressive intrathoracic disease. As in Case 1, the stimulation protocol and the muscles chosen for mapping in the postsurgical session were similar to that of the preoperative assessment. Postoperative rMT was found to be lower than the preoperative assessment [Table 1]; however, there was no substantial side difference. MEP latencies and amplitudes were within normal limits, though lower than the presurgical values. Postsurgical nTMS mapping showed no identifiable motor mapping distortion [Figure 4]. As in Case 1, GKRS did not affect or distort the original functional configuration found in the pre-GKRS nTMS examination. No motor deficit or other neurological disturbances were reported at this point, and the patient was kept on low dose corticosteroids. The corresponding structural MRI at this stage (6 months post-GKRS) revealed a limited increase in the diameter of M1 [Table 8, Figure 4], and persistent signs of ARE; M2 proved essentially unchanged at this stage. Regrettably, this last examination also revealed seven new metastases. Despite further general deterioration in the days that followed (KPS <70/RPA 3), the patient's neurological condition remained stable. No motor or sensory deficits, cognitive impairment or seizure activities were reported before succumbing to his cancer 10 months post GKRS-treatment.

## DISCUSSION

### Rationale of the study

The present paper illustrates the complexity of metastatic brain disease in motor eloquent cortex. Patients with such lesions are generally at increased risk of postsurgical neurological deterioration with reduced gross and fine motor performance in the arm and hand. Furthermore, tumors located in the rolandic and perirolandic regions remain a source of concern due to the ensuing risk of developing epileptic seizures. These patients may benefit from focal therapy such as single fraction and hypofractionated GKRS;<sup>[23,33,35,49]</sup> however, the level of risk of radiation-induced



**Figure 4:** nTMS motor mapping – pre- and post-GKRS for Case 1 and 2. nTMS motor mapping of three upper limb muscles (mAPB - green, mFDI - orange, mEDC - yellow) contralateral to the side of the stimulation. (a) Case 1 pre-GKRS nTMS. (b) Case 1 – 12 months post-GKRS nTMS. (c) Case 2 pre-GKRS nTMS. (d) Case 2 – 6 months post-GKRS nTMS.

**Table 7:** Case 1 – MRI- and LGP-verified tumor volume dynamics during treatment (GKRS 1 to GKRS 3) and up to last follow-up.

	GKRS 1 (day 1)	GKRS 2 (day 4)	GKRS 3 (day 7)	Follow-up at 1 month	Follow-up at 2 months	Follow-up at 6 months*	Follow-up at 8 months
M4 volume	7.40 cc	6.80 cc	6.40 cc	3.11 cc	0.50 cc	0.16 cc	0.12 cc

\*Follow-up MRI integrating post-GKRS nTMS. nTMS: Navigated transcranial magnetic stimulation, GKRS: Gamma knife radiosurgery, MRI: Magnetic resonance imaging, LGP: Leksell GammaPlan

**Table 8:** Case 2 – Tumor volume dynamics from the time of GKRS up to last follow-up (at 10 months).

	Stereotactic MRI (GKRS)	Follow-up at 3 months	Follow-up at 6 months (integrating postGKRS nTMS)	Follow-up at 10 months
M1 volume	5.66 cc	1.51 cc	3.17 cc**	4.8 cc**

\*\*Tumor volume increase deemed due to ARE development. nTMS: Navigated transcranial magnetic stimulation, GKRS: Gamma knife radiosurgery, MRI: Magnetic resonance imaging, ARE: Adverse radiation effect

injury to the eloquent cortex (cortical and subcortical), remains a subject of debate, particularly in the face of larger target volumes, extensive edema, and histology-surrogate factors such as radioresistance. In a prospective study by Williams *et al.*,<sup>[58]</sup> the authors reviewed 273 patients with 316 metastatic brain lesions and showed that 32% of lesions were associated with new complications. In their multivariate analysis, eloquent brain cortex location was found to be significantly associated with this type of neurological adverse event. Therefore, in the case of brain radiosurgery, careful treatment planning, aiming to protect adjacent (perilesional) functional structures, could decrease the risks of postsurgical functional deficiencies. In this two-patient case series, we successfully integrated the noninvasive neurophysiological method, nTMS, in presurgical modified dose planning. Furthermore, we used nTMS as a tool for postsurgical assessment, where the evaluation did not show any change in the location of the primary motor area of the hand suggesting the benefits of tailored dose distribution to the cortical regions. The latter was particularly the case in subject nr 2, where the patient developed an ARE post-GKRS yet without any serious neurological repercussions at long-term.

Nevertheless, the application of nTMS in radiosurgery is fairly new. Historically, the use of TMS in presurgical mapping remained limited until the availability of MRI-based neuronavigation assisted surgical series. In this context, intraoperative mapping of motor eloquent cortex under general anesthesia and speech mapping during awake surgery have generally been performed applying direct cortical stimulation (DCS); although this method is widely considered the gold standard of cortex functional mapping, its use in GKRS remains precluded by invasive requirements.

#### **nTMS and radiosurgery: what is the evidence?**

Functional mapping modalities, for example, functional MRI (fMRI),<sup>[15,52,56]</sup> magnetoencephalography,<sup>[3]</sup> and diffusion tensor imaging (DTI)<sup>[13,36]</sup> have been used as presurgical mapping tools; however, as formulated in several comparative studies, the latter modalities have method-specific limitations when compared to gold standard DCS.<sup>[14,19,28]</sup> Nonetheless, there is extensive evidence demonstrating the advantages of nTMS mapping in terms of high spatial resolution and accuracy;<sup>[27]</sup> indeed, nTMS based function mapping modalities, including nTMS-based DTI-fiber tracking, have been increasingly investigated for the purpose of providing more accurate topographic data of the perilesional OAR while optimizing the extent of resection and the outcome of microsurgery in terms of neurofunction.<sup>[7,34,40-42,51,50]</sup> Surprisingly, the advantages of the above mentioned nTMS-based modalities have not been equally utilized in the field of radiosurgery. Only a limited number of studies have described the feasibility and ulterior outcome of integrating

nTMS data onto radiosurgery planning.<sup>[6,9,20,38,46,55]</sup> In this context, we must assume that both DTI and fMRI have their inherent methodological limitations in the field of stereotactic radiotherapy; nevertheless, it is our view that nTMS data can at least be utilized as a seeding point for safe volume delineation; the latter observation has previously been discussed elsewhere.<sup>[57]</sup>

To further substantiate the above-mentioned presumptions, we feel worth discussing three pioneer studies applying nTMS alone in radiosurgical planning [Table 9]. Conti and colleagues<sup>[6]</sup> conducted a retrospective analysis on a group of patients with brain lesions in critical areas who had radiosurgery ( $n=25$ ); pre-treatment investigations included functional neuroimaging (fMRI, DTI) ( $n = 13$ ) or navigated TMS motor mapping ( $n = 12$ ). While measuring the volume of the functional motor cortex defined by either fMRI or nTMS, the study showed that the functional relevance of the cortical surface was 30% smaller than that of fMRI, leading to greater dose reduction (25%) to cortical functional areas. This indicated the clear advantage of the use of nTMS mapping over other functional imaging modalities. Later studies showed similar encouraging results. Pitch *et al.*<sup>[38]</sup> investigated 11 patients with eloquent tumors who were eligible for radiosurgery treatment. Unlike our study, the group investigated the utility of speech mapping data ( $n = 3$ ) in addition to nTMS motor mapping ( $n = 8$ ) and integrated both in radiosurgical planning. In a similar environment, Kato *et al.*<sup>[20]</sup> investigated 10 patients with arteriovenous malformation using nTMS motor and speech mapping. Successful delineation of the the affected motor cortex was reported, including the cortical areas of hypervascularization. Of note, unlike Kato *et al.*, the first two studies included patients with variable types of lesions; it is more likely that a clearer clinical advantage is demonstrated when investigating a more homogenous group of patients. In view of the underlying neurofunctional symbiosis between the corticospinal tract and the motor cortex, we propose that adding DTI to nTMS mapping could provide substantial benefits in terms of identifying a “broader” deployment of OAR, hence redirecting and optimizing dose distributions outside the target. Of note, since this feasibility study was specifically conceived to assess the technical aspects of integrating nTMS cortex motor mapping into GKRS treatment planning, we decided not to include DTI as a measure to decrease the risk of bias. However, based on the results of this study and the above drawn conclusions, combining DTI and nTMS to radiosurgery planning will potentially be the subject of a next case series.

#### **Further aspects**

As reported in this case series, both patients had metastatic brain lesions assessed as radiosensitive, yet treated with

**Table 9:** Review of literature.

Author	Patient demographics	Presurgical investigations	Postsurgical nTMS	DTI	Results	Conclusion
Conti <i>et al.</i> , 2013	(Total, <i>n</i> =25) <i>n</i> =10: AVMs <i>n</i> =3: brain metastases  <i>n</i> =12: primary tumors	fMRI and DTI-based tractography ( <i>n</i> =13)  nTMS motor mapping ( <i>n</i> =12)	No	Yes	1. 17% (average) reduction of radiation dosage to circumscribing functional areas. 2. No neurological deficit post treatment (short-term follow-up).	1. Relatively simple to integrate functional data to cyberknife treatment planning, 2. Further research is warranted to standardize and identify the limits of the procedure.
Pitch <i>et al.</i> , 2014	( <i>n</i> =11) Patients with brain lesions in presumed motor or language eloquent locations	Motor mapping ( <i>n</i> =9) Speech mapping ( <i>n</i> =2)	No	Yes	1. Improved risk-benefit balancing in all cases: (a) dose plan modification = 81.9 %, (b) reduction of radiation dosage = 72.7%, and (c) enhanced treatment indication = 63.7%.	1. nTMS data integration into presurgical planning is feasible. 2. Use of functional mapping data can improve radiosurgical planning safety for eloquently located lesions.
Kato <i>et al.</i> , 2014	( <i>n</i> =10) Patients with unruptured intracranial AVMs located in or near eloquent areas	Motor mapping ( <i>n</i> =6): perirolandic AVMs Speech mapping ( <i>n</i> =4): Left perisylvian AVMs	No	No	1. Successful delineation of the primary motor cortex in all 6 patients; plastic relocation not noticed. 2. nTMS speech mapping showed involvement of the left hemisphere in 3 patients and of the right hemisphere in 1 patient, indicating plastic changes.	1. nTMS functional mapping is feasible not only in tumorous brain lesions, but also in AVMs. 2. This method could be useful for detection of functional cortical plasticity in longitudinal studies.

nTMS: Navigated transcranial magnetic stimulation, AVM: Arteriovenous malformation, fMRI: Functional magnetic resonance imaging, DTI: Diffusion tensor imaging

two different GKRS modalities due to different tumor-surrogate and perilesional variables. Unlike previously published data,<sup>[6,20,38]</sup> we integrated nTMS mapping in post-GKRS follow-up with the aim to (i) identify possible plasticity-associated relocation of adjacent motor cortex in relation to clinical motor functional recovery and (ii) plot the degree of motor fiber damage postradiation. Although our reported cases did not show any significant plastic changes, several other studies on patients undergoing tumor resection have indeed reported postsurgical plastic relocation of the motor cortex after

3–42 months,<sup>[8]</sup> >7 months,<sup>[21]</sup> >6 months in younger patients<sup>[31]</sup> and even after multistage surgery.<sup>[54]</sup> When investigated preoperatively, Kato *et al.* reported potential plastic changes of speech eloquent cortex in the form of right hemispheric involvement of speech function; however, posttreatment changes were not investigated in this study.<sup>[20]</sup> In the case of radiosurgery, it can be debated whether plastic changes mimicking the rates described at microsurgery occur in the adult patient.<sup>[30]</sup> In our cases, the postsurgical nTMS performed 6 months postsingle-fraction GKRS (Case 2) and at 12 months



posthypofractionated GKRS (Case 1) showed largely unchanged motor mapping parameters. Most importantly, despite nTMS assisted modified dose planning, none of the patients showed any considerable motor functional disability at short- or long-term follow-up. Since different studies seem to suggest a decreased risk of ARE in hypofractionated treatments compared to single-dose GKRS,<sup>[10,17,18,22,32,47]</sup> a series of questions arise in this context: is there any correlation between the time and degree of ARE evolution and possible focal plastic redeployment? How could customized radiation schedules and potential dose-modulated immune response influence the outcome of these plastic changes? Based on our observations, we suggest that GKRS-based hypofractionated treatments (as compared to single-dose GKRS) could reduce the risk for focal plastic changes in definite settings. More studies with larger groups are warranted to confirm the latter.

## CONCLUSION

In our two patient case series, nTMS was safely and effectively integrated in single-dose and hypofractionated GKRS. Functional treatment planning based on nTMS estimates to the primary motor cortex resulted in less toxic dose distribution to the designated OAR in comparison to anatomical MRI-based GKRS planning. The latter was achieved without compromising intratumoral dose distribution. The relationship between the type of radiation schedule applied and possible subsequent long-term radiation-induced focal plastic distortions warrants further analysis. These initial data along with our review of the medical literature suggest that nTMS can be of valuable assistance in brain radiosurgery. Prospective studies involving larger, homogenous groups of patients are necessary to validate and better understand the clinical significance of nTMS in the context of GKRS-treatments in functional brain areas.

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## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms.

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## Conflicts of interest

There are no conflicts of interest.

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