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Original Article

# Application of presurgical navigated transcranial magnetic stimulation motor mapping for adjuvant radiotherapy planning in patients with high-grade gliomas

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ABSTRACT

*Background:* Navigated transcranial magnetic stimulation (nTMS) is applied in neurosurgical routine to detect motor-eloquent brain areas for safe resection of high-grade gliomas (HGGs). However, in radiation therapy (RT) planning, the primary motor cortex is not respected yet in target volume delineation. This study evaluates the implementation of nTMS motor mapping in RT planning in patients harboring motor-eloquent HGGs with the aim of reducing dose applications to the motor cortex.

*Methods:* nTMS motor maps of 30 patients diagnosed with motor-eloquent HGGs were fused with RT planning imaging and volumetric modulated RT plans were optimized using nTMS motor maps as an organ at risk (OAR). Doses to nTMS motor maps were evaluated using dose–volume histogram (DVH) parameters.

*Results:* Mean dose (Dmean) to the nTMS motor maps was 42.3 Gy (3.7–61.1 Gy) and was significantly reduced by 14.3% to 37.0 Gy (3.6–55.8 Gy, $p < 0.05$) when constraining the dose to nTMS motor areas to 45 Gy. Areas within the planning target volume (PTV) were not spared (overlap). Yet, the dose to PTV was not compromised. Even with an additional dose escalation (70 Gy) to the tumor area, nTMS motor maps can be spared by 4.6 ± 3.5 Gy (12.8%, $p < 0.05$).

*Conclusions:* nTMS motor maps can be easily implemented in standard RT planning and applied for target contouring in RT of HGGs. Doses to motor-eloquent areas can be significantly reduced when considering nTMS motor maps without affecting treatment doses to the PTV. Thus, nTMS could be used as a valuable tool in RT planning.



External beam radiation therapy (RT) is an established procedure in the multimodal therapy concept regarding the treatment of high-grade gliomas (HGGs) consisting of glioblastoma and anaplastic astrocytoma [1,2]. Maximal safe tumor resection followed by a 6-week interval of radio-chemotherapy is considered standard of care for those tumors [3,4].

Lesions in close vicinity to eloquent areas such as the motor cortex are particularly challenging regarding treatment. Since

*Abbreviations:* 3D, three-dimensional; BMRC, British Medical Research Council; BOLD-fMRI, blood oxygenation level dependent functional magnetic resonance imaging; CST, corticospinal tract; CT, computed tomography; CTV, clinical target volume; DES, direct electrical stimulation; FSRT, fractionated stereotactic radiation therapy; GTV, gross total volume; Dmean, mean dose; DTI FT, diffusion tensor imaging fiber tracking; DVH, dose–volume histogram; FLAIR, fluid attenuated inversion recovery; HGG, high-grade glioma; IMRT, intensity-modulated radiation therapy; MEP, motor evoked potential; MRI, magnetic resonance imaging; NTCP, normal tissue complication probability; nTMS, navigated transcranial magnetic stimulation; OAR, organ at risk; PTV, planning target volume; QUANTEC, quantitative analysis of normal tissue effects in the clinic; rMT, resting motor threshold; RT, radiation therapy; SIB, simultaneously integrated boost; TCP, tumor control probability; WHO, World Health Organization.

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extensive tumor removal is a prerequisite for improved survival, microsurgical resection adjacent to cortical or subcortical motor structures bears the risk of inducing lasting neurological deficits [5]. A permanent deficit in motor function not only has a significant negative impact on patients' quality of life; it is also associated with a decrease in overall survival [6]. In this context, tools like preoperative blood oxygenation level dependent functional magnetic resonance imaging (BOLD-fMRI), diffusion tensor imaging fiber tracking (DTI FT), and intraoperative electrophysiological mapping with direct electrical stimulation (DES) can help the neurosurgeon to achieve maximum tumor resection while preserving neurological function [7–10].

To date, the radiation oncologist is using computed tomography (CT) and structural magnetic resonance imaging (MRI) as well as positron emission tomography imaging for RT planning of brain tumors [11,12]. Important structures at risk that are commonly spared to prevent side effects of RT are the brainstem, optical nerves, optic chiasm, pituitary gland, and eye lenses [13,14]. Modern RT uses intensity-modulated radiation therapy (IMRT) techniques that help to deliver dose to irregular shaped target volumes while preserving areas of normal tissue [15]. However, functionally eloquent cortical areas such as the motor cortex are not routinely considered during RT planning.

Lately, navigated transcranial magnetic stimulation (nTMS) has been introduced as a novel technique for preoperative motor mapping in patients suffering from motor-eloquent brain tumors. The technique can be combined with DTI FT to become a valuable tool to enhance safe resection of brain tumors located closely to the precentral gyrus or the corticospinal tract (CST) [16–20]. For preoperative diagnostics, this technique has been demonstrated to be superior to BOLD-fMRI in delineating motor structures when compared to intraoperative DES [17,21]. This study therefore aims to systematically analyze how the dose to motor-eloquent areas can be reduced when preoperative nTMS motor maps are considered during RT planning for patients suffering from HGGs, both in conventional RT plans and with dose escalations to the primary tumor area.

## Methods

### *Navigated transcranial magnetic stimulation*

Preoperative motor mapping by nTMS was performed within the week before tumor resection. At the beginning of mapping, three-dimensional (3D) contrast-enhanced T1-weighted sequences were uploaded to a Nexstim eXimia NBS system (version 4.3.; Nexstim Plc., Helsinki, Finland). For neuronavigation during motor mapping, co-registration of the patient's head and the respective MRI sequence was performed based on anatomical landmarks, using an integrated infrared device in combination with a headband with reflective sphere markers [16,17,22]. Pregelled surface electrodes (Neuroline 720; Ambu, Bad Nauheim, Germany) were attached to upper and lower extremity muscles to record motor evoked potentials (MEPs) during stimulation.

According to current practice, the determination of the resting motor threshold (rMT) was performed first, followed by motor mapping of the tumor-affected hemisphere [16,17,22]. During mapping of cortical representations of the upper extremity, an intensity of 110% rMT was used, whereas at least 130% rMT were applied during stimulation of representations belonging to the lower extremity muscles. Post-hoc analysis was performed to distinguish between motor-positive and motor-negative points. In this context, a stimulation spot was defined as motor-positive when an MEP with an amplitude larger or equal to 50 μV was elicited, with an MEP onset latency ranging within the typical values for the upper or lower extremities. Correspondingly, a stimulation spot was regarded motor-negative when these criteria were not fulfilled. The motor-positive stimulation spots were considered as representations of motor-eloquent cortex and exported to the RT planning software, with motor-negative stimulation spots being not used further in the present study.

### *Radiation treatment planning and dose statistics*

Motor-positive nTMS spots were first merged with the contrast-enhanced T1-weighted MRI sequences within the RT planning system (Eclipse, version 13.0; Varian Medical Systems, Palo Alto, CA, USA). Motor-positive points appeared as 3D objects (Fig. 1). Preoperative MRI scans with fused motor maps were moreover fused both with the postoperative CT and MRI scans, which were acquired for RT planning during clinical routine. These MRI scans included contrast- and non-contrast-enhanced T1-weighted and fluid attenuated inversion recovery (FLAIR) sequences. Fusion was again performed within the RT software using the automatic registration function. Additional manual registration was performed in case of inaccuracy.

Afterward, the nTMS motor map of the respective patient was contoured as an organ at risk (OAR), thus delineating all motor-positive nTMS points (Fig. 1). The resection cavity plus the contrast-enhancing lesion was defined as the gross total volume (GTV). Moreover, to cover microscopic spread, 2 cm was added to the GTV and 1 cm to lesions in the FLAIR sequence, respectively, thus delineating the clinical target volume (CTV). Finally, the CTV was enlarged by 0.5 cm in regard to patient movement and minor setup errors, with the result representing the planning target volume (PTV).

Volumetric arc IMRT plans were calculated throughout. First, dose concepts of $30 \times 1.8$ Gy (59.4 Gy) were recalculated to 60 Gy total dose in single fractions of 2 Gy for better comparison. Three treatment plans were optimized for each patient. The first plan was optimized without the nTMS volume. Subsequently, treatment plans were optimized reducing the dose to nTMS motor maps as low as reasonably achievable with a dose constraint for the mean dose (Dmean) of 45 Gy (nTMS cons), but areas of nTMS motor maps within the PTV (overlap) were not spared. Then, a simultaneously integrated boost (SIB) treatment plan was optimized escalating the dose to 70 Gy (nTMS cons SIB). Plans were normalized to a median dose of 100% of the prescription dose to the PTV (60 Gy covered 50% of the target volume). Regarding SIB, the dose was normalized to a median dose of 70 Gy in the boost volume (GTV + 5 mm).

Dmean for nTMS motor maps, OARs (optic chiasm and brainstem), and the PTV were evaluated for dose statistics. In the setting of dose escalation, Dmean was determined for the PTV without the SIB volume (PTV-SIB). In addition, proportional overlaps of nTMS motor maps with PTV isodose levels (90%, 80%, 70%, 50%, and 20%) were calculated. Dose–volume histograms (DVHs) of nTMS motor maps receiving at least a specific dose were analyzed.

### *Statistical analyses*

All statistical analyses and generation of graphs were done using SSPS (version 24.0; IBM Inc., Armonk, NY, USA) or Prism (version 7.0; GraphPad Software, La Jolla, CA, USA). Descriptive statistics including mean, median, minimum, maximum, and standard deviation were calculated for patient- and tumor-related characteristics as well as doses and volumes investigated in the present study. *t*-tests for paired samples were applied to test for statistical significance between values. The level of statistical significance was set at $p < 0.05$.

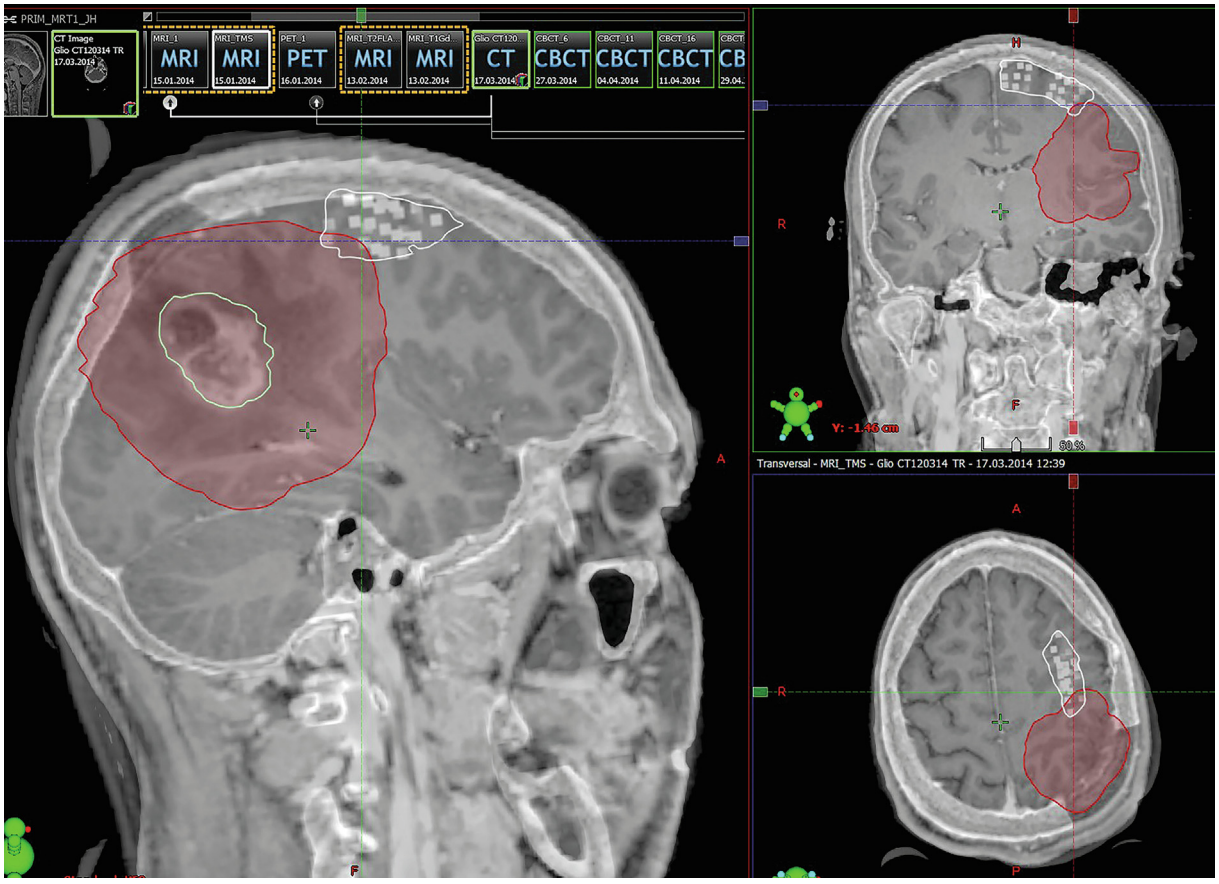


**Fig. 1.** Motor maps in target volume delineation. Motor-positive stimulation spots according to motor mapping by preoperative navigated transcranial magnetic stimulation (nTMS) are represented as white spots on T1-weighted contrast-enhanced magnetic resonance imaging (MRI) in an exemplary patient case. After import into the radiation therapy (RT) planning software, nTMS motor maps were contoured as organs at risk (OARs). The tumor is delineated in light green, the planning target volume (PTV) is depicted as a red area.

## Results

Thirty patients with HGGs in close vicinity of the motor cortex or CST were analyzed in this study (10% WHO grade III gliomas and 90% WHO grade IV gliomas; Table 1). The average maximum time to follow-up was 18.2 months (3.0–56.5 months), with all patients reaching the 3-months follow-up and 25 patients presenting for the 6-months follow-up examinations (three patients died between the 3-month and 6-month follow-up, two patients were lost to follow-up after the regular 3-month follow-up visit). When comparing motor function of the patients as measured by the British Medical Research Council (BMRC) scale between the preoperative and postoperative status, two patients improved in motor strength, whereas seven patients declined. Moreover, when comparing the preoperative status to the status during follow-up examinations six months after surgery, three patients increased in motor function and seven patients decreased. Out of the seven patients that declined in motor function between the preoperative state and 6-month follow-up, two showed radiation necrosis according to histopathological examination of probes collected during biopsy.

The nTMS motor maps were covered by the PTV by 41.2% (Table 2). The Dmean of nTMS motor maps was 42.3 Gy (3.7–61.1 Gy) and 37.0 Gy (3.6–55.8 Gy) with a constraint of 45 Gy to the motor area. Thus, Dmean to nTMS motor maps was significantly reduced by 5.3 ± 3.3 Gy (14.3%, $p < 0.05$; Fig. 2).

For SIB plans, Dmean to nTMS motor maps was decreased by 4.6 ± 3.5 Gy (12.8%, $p < 0.05$) to 37.8 Gy (Figs. 2 and 3, Table 3). Dose coverage of the PTV was not compromised when radiation dose to adjacent nTMS motor maps was restricted to 45 Gy since the PTV-Dmean was 59.9 ± 0.5 Gy vs. 59.8 ± 0.2 Gy ($p = 0.56$, Supplementary Fig. 1).

Proportional volumes of nTMS motor maps receiving a specific dose are represented in DVHs (Fig. 4A & B). The average volume of nTMS motor maps receiving equal to or more than 45 Gy and 55 Gy could be significantly reduced by 11.3% and 8.4%, respectively, with dose constraints to the nTMS motor maps ($p < 0.001$). Results are similar with an additional SIB to the GTV (Supplementary Fig. 2). There was no impact on anatomical OARs (optic chiasm and brainstem) with regard to Dmean or maximum doses with dose escalations to the GTV.

## Discussion

In this study we demonstrate that nTMS motor maps can be implemented in the RT planning of patients suffering from HGGs. So far, the primary motor cortex has not been respected as an OAR in such patients. Our results show that dose to nTMS motor maps can be significantly reduced without affecting treatment doses to the PTV.

### *Potential impact of radiation therapy on motor-eloquent brain areas*

Not only tumor resection bears the risk for neurological deficits in the management of intracerebral lesions, with RT being also capable of inducing functional impairment. For instance,

**Table 1**
Baseline patient characteristics.

| *n* | | | 30 |
|---|---|---|---|
| Gender (number of patients) | Female | | 7 |
| | Male | | 23 |
| Age at primary treatment (mean and range) | | | 57.8 years (26.9–83.5 years) |
| WHO grade (number of patients) | III | | 3 |
| | IV | | 27 |
| Tumor-affected hemisphere (number of patients) | Right | | 19 |
| | Left | | 11 |
| Extent of resection (number of patients) | >90% | | 29 |
| | >80% | | 1 |
| Adjuvant chemotherapy (number of patients) | Temozolomide | | 29 |
| | PCV | | 1 |
| Maximum tumor diameter (mean and range) | | | 4.2 cm (2.2–4.2 cm) |
| Distance tumor – nTMS motor area (mean and range) | | | 2.0 cm (0–5.5 cm) |
| Preoperative motor deficits (number of patients) | BMRC | 4/5 | 6 |
| | | ≤3/5 | 1 |
| Postoperative motor deficits (5th postoperative day, number of patients) | BMRC | 4/5 | 6 |
| | | ≤3/5 | 5 |
| Follow-up motor deficits (6 months after surgery, number of patients) | BMRC | 4/5 | 5 |
| | | ≤3/5 | 3 |

Patient and tumor characteristics for 30 patients with high-grade gliomas (HGGs) close to motor-eloquent structures. All patients received preoperative navigated transcranial magnetic stimulation (nTMS) motor mapping and were treated with radio-chemotherapy in an adjuvant setting. Motor deficits were graded according to the British Medical Research Council (BMRC) scale, tumor entity was defined by histopathological examination considering grading schemes of the World Health Organization (WHO). PCV for adjuvant chemotherapy combined procarbacine, CCNU, vincristine. Three patients died between the 3-month and 6-month follow-up, two patients were lost to follow-up after the regular 3-month follow-up visit.

**Table 2**
Spatial relation of motor maps to the planning target volume.

| | nTMS motor maps ∩ PTV | nTMS motor maps ∩ 90% isodose level | nTMS motor maps ∩ 80% isodose level | nTMS motor maps ∩ 70% isodose level | nTMS motor maps ∩ 50% isodose level | nTMS motor maps ∩ 20% isodose level |
|---|---|---|---|---|---|---|
| Mean | 41.2% | 51.2% | 57.9% | 63.8% | 75.6% | 88.8% |
| Minimum | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% |
| Maximum | 87.7% | 95.8% | 99.2% | 100.0% | 100.0% | 100.0% |
| Median | 44.2% | 64.5% | 70.2% | 77.2% | 95.5% | 100.0% |

This table shows the spatial relation of navigated transcranial magnetic stimulation (nTMS) motor maps to the planning target volume (PTV) in radiation treatment (RT) planning. nTMS motor maps were covered by the PTV in mean by 41.2% (0.0–87.7%). In four cases, there was no overlap between nTMS motor maps and the PTV. The area covered by the 90%, 80%, 70%, 50%, and 20% isodose levels was 51.2%, 57.9%, 63.8%, 75.6%, and 88.8% on average, respectively.

radio-surgical treatment of brain metastases or arteriovenous malformations close to eloquent motor or language areas can cause neurological deficits (in up to 13.5%) despite a steep dose gradient toward healthy tissue [23,24]. In the clinical setting, neurological deficits after RT appear to be mostly due to perifocal edema, tumor regrowth, and radiation necrosis close to the motor cortex or CST. The observed frequency for radiation necrosis after external beam RT of brain tumors is up to 24% [25]. With respect to the Quantitative Analysis of Normal Tissue effects in the Clinic (QUANTEC) guideline for normal tissue sparing, the probability for radiation necrosis ranges between 3 and 5% at doses between 60 and 72 Gy [26]. Since neurologic symptoms do not always resolve on steroidal medication, there might be another treatment-dependent component in the pathogenesis of motor deficits.

In RT planning, the primary motor cortex is not defined as an OAR, opposite to other structures like the brainstem or the optic chiasm, for instance. Thus, although external photon beam RT is affecting morphologically both cortical and subcortical structures, cortical motor areas are not respected when contouring target volumes [27,28]. Radiation-induced toxicity to the central nervous system is likely secondary to several mechanisms including damage to microvasculature, demyelination, deletion of stem cell populations, and alterations of cytokine expression [29,30]. Cortical atrophy comparable to neurodegenerative disease can be verified on MRI within one year after RT: both gray and white matter abnormalities can be found in humans and mice after having received cranial irradiation [31,32]. The knowledge of radiation-induced deterioration of motor function by direct impact to the cortex is scarce. However, since tumor regrowth appears to happen mainly within 6–12 months after primary treatment and the short survival of patients suffering from HGGs, the exact incidences of radiation-induced motor impairment might be masked.

### *Motor maps in radiation therapy planning*

In order to lower risks for treatment-related deficits, neurosurgeons use intraoperative mapping by DES [16,17]. This can result in safer and more complete removal of eloquent brain tumors adjacent to the precentral gyrus or CST with less perioperative trauma, leading to better outcome [18–20]. Radiation oncologists do not have such a modality yet. The mechanism of nTMS, however, is comparable to intraoperative DES and its precision now enables to outline the primary motor cortex in a standardized and accurate way. Thus, defining nTMS motor maps as an OAR and analyzing the influence in a systematic way becomes feasible.

BOLD-fMRI and DTI FT have been applied in RT planning of HGGs to reduce dose to the primary motor cortex and the CST. The use of nTMS has been analyzed for the treatment planning of

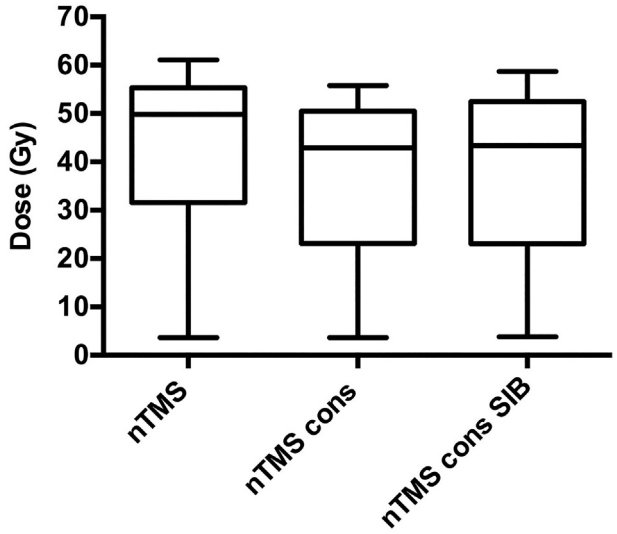


**Fig. 2.** Change of dose to motor maps. Radiation dose to the motor maps delineated by navigated transcranial magnetic stimulation (nTMS) can be significantly reduced in radiation therapy (RT) planning. Box plots are representing the doses to nTMS motor maps with minimum and maximum whiskers. In regular RT, mean dose (Dmean) is 42.3 Gy (nTMS). With dose constraints (≤45 Gy) to nTMS motor areas (nTMS cons), Dmean could be reduced by 14.3% to 37.0 Gy ($p < 0.001$). An additional simultaneous integrated boost (SIB) to the primary tumor region (nTMS cons SIB) had similar effects on Dmean on nTMS motor maps with a decrease of 12.8% to 37.8 Gy ($p < 0.001$).

radio-surgical procedures in studies including patients with brain tumors in eloquent areas [33]. Aside of an improved risk–benefit balancing in all patients, a modification of treatment plans could be demonstrated in 82%, and the dose to the target volume was reduced in 73%. However, the impact on doses to motor-eloquent structures applying nTMS has not been analyzed in patients with HGGs to date. Thus, the present study is the first to demonstrate the potential benefit of nTMS motor mapping in IMRT planning of HGGs to decrease the radiation dose to the motor cortex, as outlined by nTMS motor mapping, without affecting treatment dose to the PTV.

All enrolled patients received doses of 60 and 59.4 Gy, respectively. With respect to a considerable infiltrating zone of HGGs, the CTV is fairly large. Therefore, concerning standard RT planning, sparing the motor cortex is a challenge. Both the PTV and the 90% isodose level cover nTMS motor areas by 41.2% and 51.2% on average, respectively. Consequently, nTMS motor maps are receiving fairly high doses on average. Dmean is 42.3 Gy and the volume of nTMS motor maps receiving equal to or more than 50 Gy is 45%. Regarding the primary motor cortex as an OAR, nTMS motor mapping can help the radiation oncologist to significantly decrease Dmean of nTMS motor maps by 14.3% without negatively affecting doses to the PTV. Of note, there was no dose restriction to the PTV when sparing any nTMS motor areas outside of the PTV (59.9 ± 0.5 Gy vs. 59.8 ± 0.2 Gy, $p = 0.54$), even in the setting of an dose escalation to the GTV (Supplementary Fig. 1).

Looking at DVH curves, the volume of nTMS motor maps receiving a specific dose could be significantly reduced, represented by a steeper curve gradient for a dose range from 10 to 45 Gy; however, regarding higher doses, the effect seemed subtle (Fig. 4A & B). However, even within a high dose range, constraints to nTMS motor areas were beneficial with a significant decrease regarding 45 Gy, 50 Gy, and 55 Gy (Supplementary Fig. 2). Dose escalation has been subject of several treatment studies among patients harboring HGGs with controversial results [34,35]. In the setting of dose escalation considering SIB up to 70 Gy to the primary tumor region a reduction in radiation by 13% to the motor areas can be achieved.

RT planning using nTMS motor maps could help to reduce the dose to the motor cortex in the primary RT, although the motor cortex appears to be morphologically rather insensitive to RT as compared to language-eloquent areas and regions of high-order cognition as the temporal and limbic cortex [36]. This goes along with the observation that cognitive impairments affecting memory, attention, and executive functions are more frequent than palsies or sensory deficits. The incidence of radiation necrosis is significantly associated with total dose and chemotherapy [37]. Therefore, the risk for radiation necrosis especially in RT in recurrent disease could be reduced since tumor regrowth in most cases happens in the area of the primary tumor site and in or close to the resection cavity [38]. Although recurrent RT is applied in

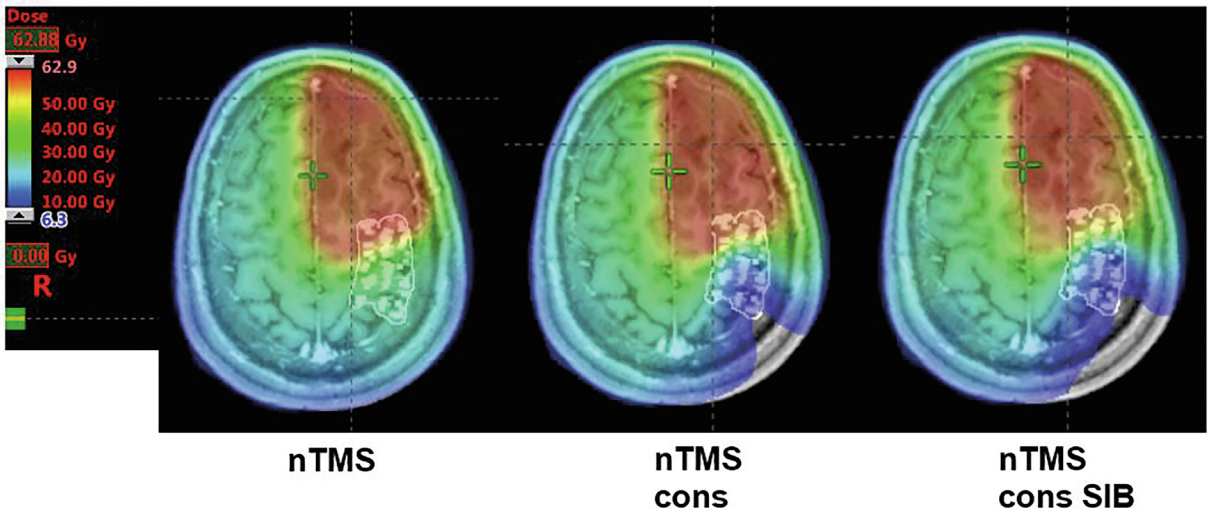


**Fig. 3.** Dose distribution within motor maps considering appropriate dose constraints. This figure illustrates the external beam plan for radiation therapy (RT) planning in one patient with a glioblastoma multiforme affecting the frontal lobe. Motor-positive stimulation spots as derived from motor mapping by navigated transcranial magnetic stimulation (nTMS) are represented as white spots on T1-weighted contrast-enhanced magnetic resonance imaging (MRI). After importing into the RT planning software, nTMS motor maps were contoured as organs at risk (OARs). Dose distribution is depicted in color-wash mode, with high doses depicted in *red* and low doses shown in *blue*. nTMS motor-positive stimulation spots are partially situated within the high dose range for a regular RT plan (nTMS). Dose constraints to nTMS motor maps resulted in a shift of dose distribution to lower values (nTMS cons), which was also found for additional simultaneous integrated boost (SIB; nTMS cons SIB).

**Table 3**
Relative and absolute change of dose to motor maps.

| nTMS motor maps | Absolute change of Dmean nTMS cons | Relative change of Dmean nTMS cons | Absolute change of Dmean nTMS cons SIB | Relative change of Dmean nTMS cons SIB |
|---|---|---|---|---|
| Mean | −5.3 Gy | −14.3% | −4.6 Gy | −12.8% |
| Minimum | 0.0 Gy | −1.4% | +0.6 Gy | +3.8% |
| Maximum | −12.6 Gy | −45.3% | −12.1 Gy | −43.6% |
| Median | −4.9 Gy | −10.6% | −3.9 Gy | −7.4% |

The relative and absolute change of the mean dose (Dmean) in navigated transcranial magnetic stimulation (nTMS) motor maps is depicted in this table. When applying constraints to nTMS motor maps (nTMS cons), an average reduction of 5.3 Gy (14.3%) could be accomplished. There was one case with only a minor reduction of 0.05 Gy. With an additional simultaneously integrated boost (SIB) to the primary tumor region (nTMS cons SIB), there was still a decrease in Dmean of 4.6 Gy (12.8%). However, in three cases, a slight increase of the Dmean was observed.

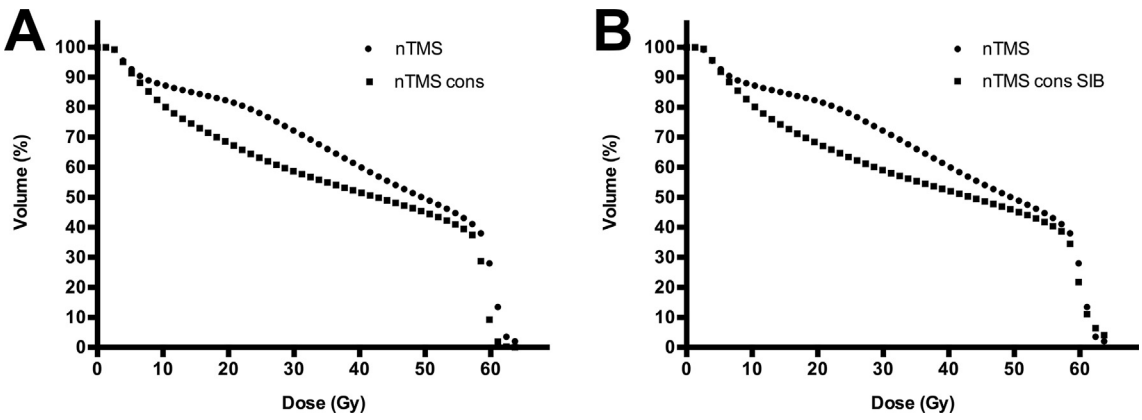


**Fig. 4.** Dose–volume histogram (DVH) curves for motor maps. Proportional volume of motor maps by navigated transcranial magnetic stimulation (nTMS) receiving a specific dose represented in DVHs. Applying dose constraints to nTMS motor maps (nTMS cons) reduced nTMS motor map volumes receiving doses > 10 Gy, as represented by a steeper gradient of DVH curves compared to standard treatment planning (nTMS). The best effect can be observed in a dose range from 15 to 45 Gy. This effect is ceasing for higher doses due to partially high overlap of the planning target volume (PTV) and nTMS motor maps (*A*). The same effect can be observed with additional dose escalation by simultaneous integrated boost (SIB) to the primary tumor area (nTMS cons SIB; *B*).

stereotactic techniques with a precision of approximately 1 mm, there is still a potential risk for direct subsequent neurologic impairment, which could be reduced by using techniques like nTMS for RT planning. The beneficial effect of nTMS motor maps for highly conformal RT techniques such as linear-accelerator based fractionated stereotactic radiation therapy (FSRT) or gamma knife radiosurgery has been demonstrated [39,40]. For gamma knife radiosurgery of brain lesions nTMS helped to reduce dose to critical cortical areas in average by 25% [39]. Our group showed that nTMS is applicable for postsurgical FSRT planning after resection of brain metastases with promising results. In 30 patients harboring supratentorial brain metastases dose to nTMS motor maps has been reduced by 18.1% on average, but without simultaneous reductions in dose to the PTV [40].

In the light of functional data, nTMS motor mapping is a reliable and easily applicable alternative to BOLD-fMRI for better sparing eloquent brain areas. Since BOLD-fMRI detects disparities in oxygen levels between different areas of the brain, signals can be impaired by the tumor itself secondary to its oxygen consumption from adjacent brain regions [41]. Subsequently, it seems to be less accurate and reliable for outlining function in brain tumor patients when compared to nTMS mapping [17,21].

Defining the PTV according to the general contouring guidelines results in a significant overlap of the PTV with the nTMS motor map in some cases; therefore, the potential dose reduction can be subtle whereas the impact on neurologic function might be relevant. However, looking at favorable constellations with minimal interference of the PTV and nTMS motor maps, dose reductions of up to 45% could be observed. Thus, at least a subset of patients could benefit from the use of nTMS motor maps in RT planning, especially in the setting of tumor recurrence and the need for recurrent RT.

## Limitations

In this study presurgical nTMS motor maps were fused with postsurgical anatomical scanning to generate nTMS-adapted RT plans. A perioperative brain shift, depending on original tumor size, the volume of resection, and perilesional edema could cause a shift that makes the fusion potentially imprecise. Usually the time from surgery to the beginning of RT is more than two weeks and often up to six weeks. During this period, most effects, such as brain shift from edema, should have vanished. However, postsurgical nTMS motor maps should be applied in prospective follow-up studies, with data from such studies being highly needed to confirm the initial results of the present investigation. Furthermore, the real impact of standard RT dose of 60 Gy to motor-eloquent cortical regions or the CST remains mostly unclear, and studies highlighting this issue are scarce. Still, the real effect might be masked by short survival time and early tumor recurrence. Thus, comparison with other tumor entities is challenging since they preferentially would present with longer survival and are mostly treated with other RT protocols. The distinct impact of radiation to functional cortical regions should be addressed in future studies. Moreover, normal tissue complication probability (NTCP)/tumor control probability (TCP) algorithms could help to address this issue for larger cohorts with appropriate follow-up time.

Despite relevant limitations, this study demonstrates the feasibility of using nTMS motor maps for RT planning in patients suffering from HGGs, and it furthermore reveals that doses to parts

of the nTMS motor maps and, thus, motor-eloquent cortex that are located outside of the PTV can be significantly reduced without affecting the treatment doses to the PTV. Based on these results, the potential benefit of nTMS mapping in RT planning of malignant brain tumors has to be further investigated in prospective trials using postoperative nTMS motor maps.

## Declarations

Ethical approval and consent to participate

The experimental setup was approved by the local ethics committee of our university (registration number: 5883/13) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

## Consent for publication

Not applicable.

## Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Competing interests

NS received honoraria from Nexstim Plc (Helsinki, Finland). SK is consultant for Nexstim Plc (Helsinki, Finland) and received honoraria from Medtronic (Meerbusch, Germany) and Carl Zeiss Meditec (Oberkochen, Germany). SK and BM received research grants and are consultants for Brainlab AG (Munich, Germany). BM received honoraria, consulting fees, and research grants from Medtronic (Meerbusch, Germany), icotec ag (Altstätten, Switzerland), and Relievant Medsystemy Inc. (Sunnyvale, CA, USA), honoraria and research grants from Ulrich Medical (Ulm, Germany), honoraria and consulting fees from Spineart Deutschland GmbH (Frankfurt, Germany) and DePuy Synthes (West Chester, PA, USA), and royalties from Spineart Deutschland GmbH (Frankfurt, Germany). However, all authors declare that they have no conflict of interest regarding the materials used or the results presented in this study.

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## Authors' contributions

CD: experimental design, data acquisition, data handling, data analysis including statistics, data interpretation, literature research, drafting of the manuscript, read and approved final version.

MS: data acquisition, data handling, data analysis including statistics, data interpretation, read and approved final version.

NS: experimental design, data acquisition, data handling, data analysis including statistics, data interpretation, literature research, drafting of the manuscript, read and approved final version.

MO: data acquisition, data handling, data analysis including statistics, data interpretation, drafting of the manuscript, read and approved final version.

BM: experimental design, data acquisition, data handling, study supervision, read and approved final version.

SC: experimental design, data acquisition, data handling, study supervision, read and approved final version.

SK: experimental design, data acquisition, data handling, data interpretation, literature research, drafting of the manuscript, study supervision, read and approved final version.

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## Authors' information

CD is a resident, MO a physicist, and SC is head of the Department of Radiation Oncology. MS is a medical student. NS is a resident at the Department of Diagnostic and Interventional Neuroradiology. SK is an attending, and BM is head of the Department of Neurosurgery.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.04.029.

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