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Preoperative navigated transcranial magnetic stimulation in patients with motor-eloquent brain lesions

Präoperative navigierte transkranielle magnetische Stimulation bei Patienten mit motor-eloquenten zerebralen Raumforderungen

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Für Frank

Tú vives siempre en tus actos.
La vida es lo que tú tocas.

De tus ojos, sólo de ellos,
sale la luz que te guía
los pasos. Andas
por lo que ves. Nada más.

Tú nunca puedes dudar.

Y nunca te equivocaste,
más que una vez, una noche
que te encaprichó una sombra.
Y la quisiste abrazar.
Y era yo[1].

[1] Pedro Salinas, La voz a ti debida (gekürzt).

Contents

Deutsche Zusammenfassung

Die navigierte transkranielle Magnetstimulation des Motor-Kortex ist eine nicht-invasive Technik, die eine präoperative Kartierung motor-eloquenter kortikaler Areale erlaubt. Die Einbeziehung dieser Information bei der Resektion motor-eloquent gelegener Hirnläsionen soll eine bessere Resektionsrate ermöglichen, ohne die motorische Funktion zusätzlich zu schädigen.

Um diese Hypothese zu überprüfen, wird in dieser Arbeit retrospektiv das Kollektiv von Patienten mit durchgeführter nTMS-Kartierung des Motor-Kortex untersucht, die seit der Einführung der nTMS-Technik im Juni 2013 bis Ende des Jahres 2018 an der Klinik für Neurochirurgie operiert wurden (nTMS-Gruppe). Dies waren insgesamt 127 Patienten mit motor-eloquenten zerebralen Raumforderungen (Gliome, Metastasen, Meningeome und Kavernome). Ein Kontroll-Kollektiv von 379 Patienten mit Läsionen aus der gleichen Entitätsgruppe, die zwischen 2009 und 2018 ohne nTMS-Untersuchung behandelt wurden, wurde retrospektiv erstellt. Aus diesem wurde ein 1:1 Match-Kollektiv gebildet (Kontroll-Gruppe). Das Outcome beider Kohorten wurde anhand der Parameter Kraftgrad, Resektionsstatus, Größe der Kraniotomie, OP-Dauer und Krankenhausaufenthalt verglichen.

Nach durchgeführtem Pair-matching zeigten sich zwei homogene Kollektive mit vergleichbarer Demographie (Alter, Geschlecht), präoperativer motorischer Funktion und Hirnläsionen (Histologie, Lokalisation, Tumorgröße). In der nTMS-Gruppe konnte signifikant häufiger eine Komplettresektion erreicht werden als in der Kontroll-Gruppe (84,3 % vs. 73,2 %, $p = 0,02$), wobei die motorische Funktion in beiden Gruppen vergleichbar war. Die Größe der Kraniotomie, OP-Dauer und der Krankenhaus-aufenthalt waren in beiden Gruppen ebenfalls vergleichbar.

In der Subgruppen-Analyse getrennt nach Histologie zeigte sich, dass die signifikant verbesserte Resektionsrate durch die Subgruppe der malignen Gliome WHO°III/IV abgebildet wurde (nTMS-Gruppe 72,3 % vs. Kontroll-Gruppe 53,2 %, $p = 0,049$). Daher wurde das Gesamtüberleben der Patienten mit malignen Gliomen untersucht. Die univariate Analyse zeigte eine prognostische Assoziation des Gesamtüberlebens mit den Parametern Patientenalter < 60 Jahren, Komplettresektion und Intaktheit des motorischen Systems (keine präoperative Parese). In der multivariaten Analyse

zeigten sich Patientenalter und Komplettresektion als unabhängige Faktoren für ein signifikant verbessertes Überleben bei Patienten mit malignen Gliomen.

Prädiktoren für das Erreichen einer Komplettresektion waren in der multivariaten Analyse die Verwendung der präoperativen nTMS-Kartierung, die präoperative motorische Funktion und die Tumorgröße.

Für die Subgruppen der Patienten mit Metastasen, Meningeomen und Kavernomen konnten keine Unterschiede bezüglich der Resektionsrate, postoperativen motorischen Funktion, Kraniotomiegröße, OP-Dauer oder Krankenhausaufenthalt festgestellt werden.

In Zusammenschau zeigen die Ergebnisse, dass in der Subgruppe der malignen Gliome mit Hilfe der nTMS-Kartierung eine signifikant bessere Resektionsrate erreicht wird, ohne die motorische Funktion hierbei zu beeinträchtigen. Die verbesserte Resektionsrate ist ein kritischer Faktor für das Überleben von Patienten mit malignen Gliomen. Die Implementierung der nTMS-Kartierung in die Resektion motor-eloquenter Läsionen, insbesondere maligner Gliome, kann daher zu einem verbesserten chirurgischen Ergebnis und verbesserter Prognose dieser Patienten beitragen.

Abstract

Navigated transcranial magnetic stimulation (nTMS) of the motor cortex is a non-invasive technique which allows for preoperative determination of motor-eloquent cortical areas. Including this information into surgical planning of motor-eloquent brain lesions is expected to allow for better resection rates while preserving motor function.

To test this hypothesis, this thesis retrospectively evaluates all patients receiving preoperative nTMS mapping of the motor cortex at the Department of Neurosurgery since its introduction in June 2013 to December 2018 (nTMS-group). This group includes 127 patients with motor-eloquent brain lesions (glioma, metastases, meningioma and cavernoma). A control collective of 379 patients with lesions of the same entities, who were treated between 2009 and 2018 without nTMS-mapping, was retrospectively established. Out of this group, a 1:1 match collective was selected (control group). The outcome of both cohorts was compared with respect to motor function, resection status, craniotomy size, duration of surgery, and hospital stay.

Pair-matching demonstrated a homogeneous distribution of demographic characteristics (age, sex), preoperative motor function, and brain lesion (histology, location, tumour size). In the nTMS-group gross total resection was achieved significantly more frequently (84.3 % vs. 73.2 %, p = 0.02), while motor outcome was similar in both groups. Size of craniotomy, duration of surgery and hospital stay were also comparable in both groups.

The subgroup analysis by lesion entity shows that the significantly improved resection rate mainly originates from the subgroup of malignant glioma WHO°III/IV (nTMS group 72.3 % vs. control-group 53.2 %, p = 0.049). Consequently, overall survival was analysed for patients with malignant glioma. Univariate analysis demonstrated a prognostic effect of patient age < 60 years, resection status, and intact motor function (no preoperative paresis). In the multivariate analysis, patient age and gross total resection were independently associated with survival of patients with malignant glioma.

Multivariate analysis demonstrated that the use of preoperative nTMS-motor mapping, better preoperative motor function and comparatively smaller brain lesions were independent prognostic factors for achieving gross total resection.

The subgroups of patients with metastases, meningiomas and cavernous malformations did not show any differences for gross total resection rate, postoperative motor function, craniotomy size, duration of surgery or hospital stay between the nTMS and control groups.

Taken together, the results highlight that in the subgroup of patients with malignant glioma, preoperative nTMS-mapping of the motor cortex allows for significantly improved gross total resection rates without compromising motor outcome. The increased resection rate is a critical factor for the survival of patients with malignant glioma. Hence, implementing nTMS-mapping in the resection of motor-eloquent brain lesions, particularly malignant glioma, contributes to better surgical outcome and likely improved prognosis.

1. Introduction

The surgical therapy of peri-rolandic cerebral tumours strives for maximum tumour resection while preserving motor function. Therefore, the identification of functional cortical areas is critical to allow for appreciation of spatial relationships between functional areas and tumour tissue.

The gold standard for mapping of the cortical motor area is intraoperative direct cortical electrical stimulation (DCS) requiring craniotomy and brain parenchyma exposure [6].

Preoperative planning of the surgical approach and extent of resection must rely on non-invasive methods. Functional magnetic resonance imaging (fMRI) has been applied to visualize brain areas involved in motor, language or other functional tasks in healthy individuals. However, this technique relies on changes in the cerebral blood supply and metabolism. Both metabolism and vasculature are changed in and surrounding brain tumours, which poses a problem for fMRI in brain tumour patients [15;50]. Furthermore, fMRI imaging does not provide a direct cortical functional map, but merely illustrates blood oxygen level dependent signal alterations to a specific task.

Within the past decade, navigated transcranial magnetic stimulation (nTMS) has been implemented into the field of neurosurgery. This non-invasive technique makes use of magnetically elicited stimulation in cortical neurons for preoperative mapping of the primary motor cortex and other functional areas. Since the electrophysiological approach is identical to direct cortical stimulation, this method expectedly provides comparable motor maps for surgical planning [36;57].

A small number of studies have demonstrated the value of pre-surgical nTMS mapping of the motor cortex [8;20-22;36-39;41-42;56]. nTMS implementation has been associated with improved tumour resection rates in patients suffering from motor-eloquent brain lesions, while motor function was preserved or even improved in the postoperative course. However, the presently available evidence is scarce: to date, only two studies have presented comparative cohort studies with over 100 patients.

Further substantiation of the usefulness of nTMS-based motor mapping in brain surgery is required.

At the Department of Neurosurgery of Saarland University Medical Center, preoperative nTMS mapping of the motor cortex was introduced in June 2013 and has hence routinely been performed in patients undergoing surgical resection of motor eloquent brain lesions. The aim of this thesis is to retrospectively evaluate the institutional database of patients from an over 5 years' cohort. Comparison to a matched cohort of historical control patients who had no preoperative nTMS information available was performed to evaluate the role of preoperative nTMS in motor-eloquent brain surgery.

2. Background and Theory

2.1. Transcranial magnetic stimulation (TMS)

2.1.1. Physical and physiological principles

Non-invasive magnetic stimulation of the human motor cortex was first described in 1985 by Barker, Jalinous and Freeston [1]. Identically to direct cortical stimulation (DCS), activation of cortical neurons in this technique is achieved by an electric field; however, this field is not directly applied to the cortex, but created non-invasively by induction from a magnetic field. The magnetic field is created by a current pulse through a magnetic coil placed above the scalp [16;45] (Figure 1).

The magnetic pulse creates a potential difference resulting in ion flow in the brain. The cellular effect of the electric current is the alteration of the membrane potential, which is most pronounced at bends or terminations of axons or dendrites. In principle, TMS can thus be considered directly reciprocal to magneto-encephalography (MEG), in which an external coil is used to detect changes in the magnetic field induced by currents flowing in the brain [48].

Stimulation of the motor cortex is achieved by single magnetic pulses applied over the presumed location of the primary motor area. With sufficient stimulus intensity, an action potential is created in the cortical motoneurons, which extends along the corticospinal tract and activates α-motoneurons in the spinal cord. A motor-evoked potential (MEP) is generated in the corresponding muscle, which can be measured by continuous electromyography (EMG) monitoring [23].

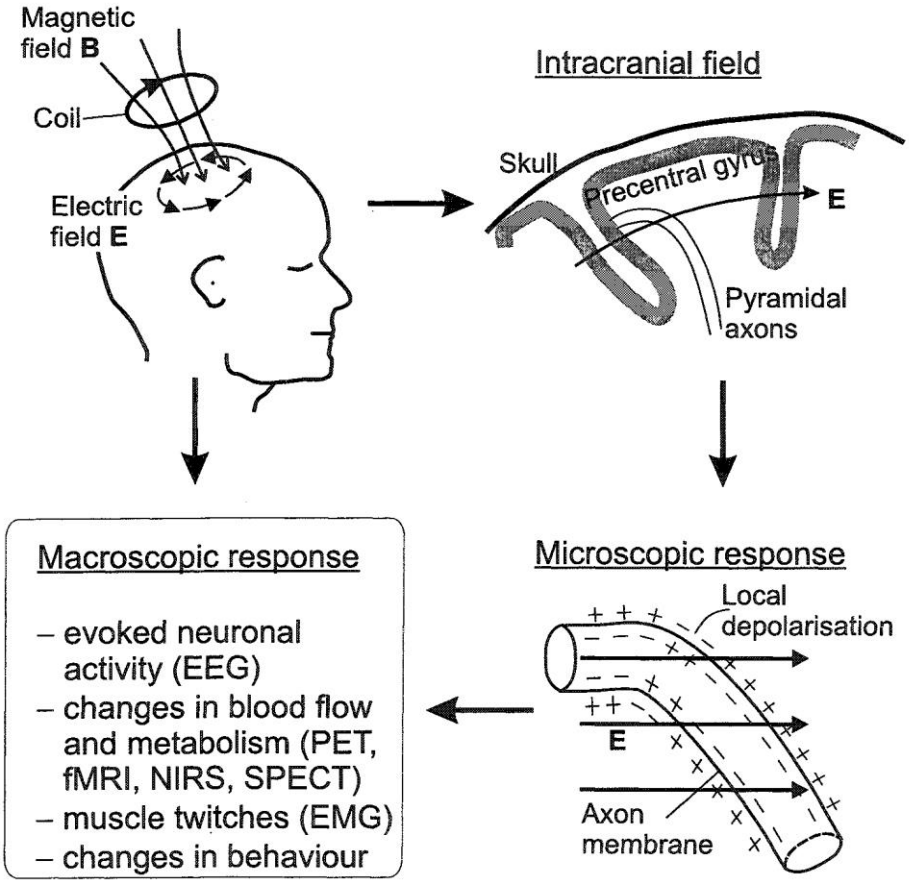


Figure 1. Principle of transcranial magnetic stimulation [16]

2.1.2. Navigation in TMS

A break-through in the clinical applicability of TMS was the introduction of neuro-navigation. In modern navigated TMS (nTMS) systems, a high-resolution structural MRI is acquired prior to mapping. For mapping, a head tracker carrying infrared (IR) markers is attached to the patient's head and monitored by a pair of IR cameras. The surface of the head and face is digitally reconstructed by moving a marker pen with IR markers to several pre-defined anatomical landmarks and co-registered with the skin surface as determined from the MRI. In this way, the brain anatomy imaged by MRI

can be correlated with the skin surface. As the coil also carries IR markers, its position relative to the patient's scalp and brain can be tracked in real time [25;46].

Using the individual MRI information, the instantaneous electric field inside the patient's brain during magnetic stimulation can be calculated. When an answer to a stimulus is detected, the focus of the stimulating field is projected onto the cortical surface and saved as eloquent point in the MRI dataset [49;52]. By repeated stimulations, a map of motor-eloquent points for different muscle groups can thus be established. This can be evaluated when choosing the surgical approach and can also be included for intra-operative navigation. Details of the mapping procedure are provided in the Methods section.

2.2. Brain tumours and lesions

Brain tumours can be classified into primary brain tumours that arise from the neuroectoderm of the central nervous system (CNS) and secondary brain tumours, i.e. metastases of tumours with different histologies elsewhere in the body. Intra-axial tumours are located within the parenchyma, while extra-axial tumours are located intracranially, but outside the brain parenchyma. This section gives a short outline of the most common types of brain tumours relevant for this thesis. Although cavernous malformation are not neoplastic lesions, they were also included in the study collective since they are surgically treated similarly to brain tumours, so they are shortly presented at the end of this chapter.

2.2.1. Gliomas

Gliomas, the most prevalent primary tumours of the CNS, share histologic characteristics of glial cells. According to the 2007 World Health Organization (WHO) classification, they were hence classified based on their phenotype as astrocytic, oligodendroglial, oligoastrocytic, ependymal, neuronal or mixed neuronal-glial tumours [26]. The revised classification of 2016 incorporates molecular-genetic characteristics into a new combined phenotypic and genotypic diagnosis [19;27;60]. In this new classification, diffusely infiltrating gliomas include astrocytoma WHO°II and III, grade II

and II oligodendroglioma, glioblastoma multiforme (WHO°IV) and the diffuse childhood gliomas. All these neoplasms are characterised by invasion of the surrounding parenchyma, and are distinguished by several genetic alteration such as mutation status of isocitrate-dehydrogenase 1 (IDH1), 1p/19q codeletion (oligodendroglioma), loss of ATRX or TP3 mutation.

Diffuse astrocytomas WHO°II are low-grade gliomas (LGG) of differentiated cells without signs of anaplasia. They mainly occur in young adults and can become symptomatic with epileptic seizures, focal deficits, headache or nausea, but can also remain largely asymptomatic. In T1-weighted MRI, LGG present as hypointense lesions; in fluid attenuated inversion recovery (FLAIR) sequences, hyperintensities represent tumour-infiltrated brain tissue [63]. Subsequent genetic alterations can transform these tumours into malignant astrocytoma WHO°III or glioblastoma.

The most commonly occurring high-grade gliomas WHO°III are anaplastic astrocytomas, which mostly arise from diffuse astrocytomas WHO°II. These tumours present signs of cell anaplasia and pleomorphism, atypical nuclei and increased proliferation. The disruption of the blood-brain barrier associated with these tumours results in contrast-enhancing hyperintense lesions in MRI, which often show a mixed composition of low- and high-grade regions [63].

The glioblastoma multiforme (GBM) (WHO°IV astrocytoma) is the most frequent malignant brain tumour in adults. It is characterized by diffuse infiltration and cell migration, necrotic areas, neovascularization and extreme cellular atypia. GBM can arise as a secondary glioblastoma by upgrade from a lower-grade astrocytoma, typically exhibiting IDH1-mutation, or as a *de novo* entity (“primary GBM”, usually IDH wildtype), where IDH1-mutation status is associated with improved prognosis. In MRI, GBM are characterized by an inhomogeneous three-phasic composition: necrotic core, ring-shaped contrast enhancement and surrounding edema. From a predictive point of view a relevant biomarker of GBM is the methylation status of the MGMT (O6-methylguanin-DNA-methyl transferase) promoter, which is associated with improved response to temozolomide chemotherapy and hence improved prognosis under temozolomide therapy [63].

2.2.2. Meningiomas

Meningiomas are the second most frequent neoplasias of the central nervous system (35 % of adult intracranial neoplasia), taking their origin from the meninges. In most cases, they are benign and grow slowly by compressing and displacing surrounding tissues while retaining their attachment to the dura (“dural tail”). As extra-axial tumours, their preferred locations are above the frontal and parietal lobes (parasagittal and convexity meningioma), sphenoid ridge, olfactory groove, suprasellar, falx cerebri, cerebellopontine angle, and the spinal cord. Owing to their slow growth, they also tend to have a benign clinical course with varying perifocal edema and homogeneous contrast enhancement in MRI. Their pronounced vascularization can be visualized by angiographic methods, and they often show extensive calcification visible on X-ray images or computed tomography (CT) [30;31;63].

2.2.3. Metastases

It is estimated that 10-30 % of patients with cancer develop brain metastases, which make up the majority of intracranial adult neoplasms. The largest proportion of brain metastases arises from lung cancer, followed by breast cancer, malignant melanoma, prostate cancer, colorectal carcinoma and renal cell carcinoma. The symptoms of intracerebral metastases cannot be differentiated from those of fast-growing primary brain tumours, including signs of increased intracranial pressure, epileptic seizures, focal symptoms, and personality changes. The typical presentation of metastases in MR imaging is as ring-shaped contrast-enhancing lesions, often around a necrotic core, with extensive edema. 18-Fluor-desoxy-glucose (18-FDG) positron emission tomography (PET) and single-photon emission computed tomography (SPECT) using radioactively labelled amino acid analogues can help distinguish eventual relapse/reoccurrence from radionecrosis [28;63].

2.2.4. Cavernomas

Cavernomas (cavernous angioma, cavernous haemangioma or cerebral cavernous malformations) do not belong to cerebral neoplasms. Yet they are included in this overview since their macroscopic presentation is in the form of a spherical mass

(“mulberry” or “popcorn-like” lesion in MRI) and the surgical approach is resection very similar to the neoplastic brain lesions described above. Histologically, cavernomas consist of pathological dilated and hyalinised capillaries with thin vessel walls and extended lumen. They are often surrounded by gliosis and microhemorrhages, which can be visualized as hemosiderin deposit ring in MRI. Thrombotic stenoses or calcifications also occur. While often asymptomatic, cavernomas pose the risk of epilepsy or bleeding. Once symptomatic, surgery demands resection of both the cavernoma itself and the hemosiderin gliosis to achieve disease-control [63-64].

3. Patients and Methods

3.1. Patient collective

3.1.1. nTMS patients

Preoperative nTMS mapping of the motor cortex for motor-eloquent brain lesions was introduced at the Department of Neurosurgery in June 2013. All patients with preoperative nTMS motor-mapping from 06/2013 until 12/2018 were retrospectively reviewed irrespective of lesion type.

For all patients, demographic data, histology, surgery time, complications during surgery, duration of hospital stay and follow-up were retrieved from the clinical information system (SAP SE, Walldorf, Germany). Motor function was evaluated preoperatively and at two postoperative time points (at discharge, about one week after surgery = post-operative day 7 (POD 7), and during outpatient follow-up between 6 and 10 weeks post-surgery, average POD 60) and was classified according to the British Medical Research Council (BMRC) ranking as

0	complete paresis
1	muscle twitching without movement
2	movement possible, but not overcoming gravity
3	movement against gravity
4	movement with reduced strength lowering of the arm or leg in forward extension test
4+	almost full strength no lowering, but pronation of the arm in forward extension test
5	full strength.

BMRC ranks 0-3 were considered as “severe pareses” and ranks 4-4+ as “mild paresis”. Postoperative motor function was furthermore classified as “improved”, “unchanged” or “worse” and any deterioration in motor function after surgery was defined either as temporary or permanent paresis, depending on whether or not the motor function returned to the preoperative baseline.

The imaging data in the PACS (picture archiving and communication system) database (Sectra IDS7, Sectra AB, Linköping, Sweden) was reviewed to assess motor-eloquence of the lesions. Motor-eloquence was assigned if the lesion infiltrated the precentral gyrus or corticospinal tract, or if the tumour mass effect caused significant distortion of the anatomy, such that the gyri and sulci could not be discriminated. In the preoperative images, the 3D-lesion diameters and volumes were measured based on contrast-enhanced T1-weighted sequences and edema diameters and volumes based on the T2 fluid-attenuated inversion recovery (FLAIR) sequence. Additionally, the localization of the lesion mass was either assigned as primarily frontal or parietal. Follow-up images were reviewed to determine whether gross total resection (GTR) was achieved and whether and when recurrence/relapse occurred. The primary outcome variable GTR was only assigned if it was independently confirmed by an attending neuroradiologist.

The diameter of the craniotomy was measured on postoperative cranial computed tomography (CT) images. For all patients, any given adjuvant treatment regimen was extracted from the medical records. To determine 18-months survival of malignant glioma patients, outpatient follow-up and their detailed documentation were analyzed.

Patients were excluded if lesions were deemed non-motor-eloquent, in case preoperative nTMS stimulation had failed, patients < 18 years, and patients with lack of follow-up that allowed primary outcome analysis of GTR and motor outcome. A total of 137 nTMS patient datasets were retained for the analysis; images of exemplary lesions are shown in Figure 2. Demographic data are presented together with the matched cohort in the next chapter.

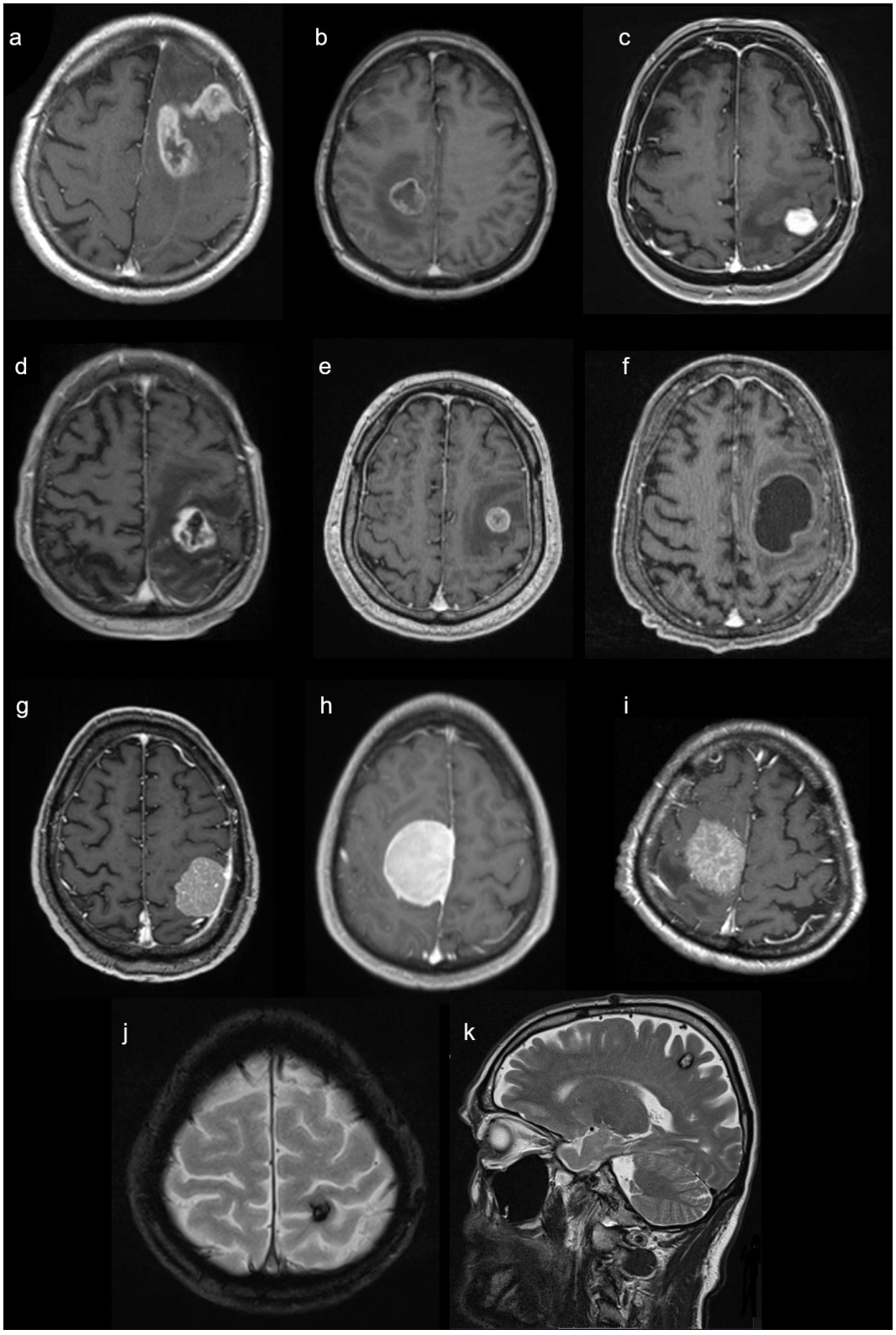


Figure 2. Example patients from the nTMS collective with different lesion entities. a-c: GBM (T1 with contrast dye), d-f: metastasis (T1 with contrast dye), g-i: meningioma (T1 with contrast dye), j-k: cavernoma (T2* and T2)

3.1.2. Matching of non-nTMS control patients

First, a retrospective dataset of possible match candidates was established with the aim of obtaining about 3 potential matches per nTMS patient. To create this dataset, all potential motor-eloquent brain surgeries in the period between 2006-2018 were reviewed by lesion entity. This included a subset of patients between 2013-2018 that had not undergone nTMS mapping due to organizational reasons.

Match patients were retrieved from the database separately for the entities

- glioblastoma
- high grade glioma WHO°III
- low grade glioma WHO°II
- metastasis
- meningioma
- cavernoma
- other: arterio-venous malformation, lymphoma, abscess, rare cerebral tumours

Therefore, an ideal histological match was obtained, since entities were congruent.

For each potential match candidate, the preoperative MRI was reviewed for lesion localization, size and edema to determine the ideal nTMS-case correlate. In addition, preoperative motor function was matched closely not allowing deviation of BMRC grades > 2. In this way, a total of 407 potential matches were established.

Out of this cohort of potential matches, 1:1 pair-matching was manually performed based on lesion etiology/histology, preoperative motor function, lesion location with respect to the motor cortex (pre- or post-central, i.e. lesion mass either frontal vs. parietal), lesion diameter and volume. In case two candidates performed equally well in all these criteria, edema diameter and volume were also matched. Age and sex were secondary match variables with minor priority.

During this process, it was found that entities other than glioma (WHO°II-IV), metastasis, meningioma and cavernoma proved difficult to match. Furthermore, other lesions provided considerable heterogeneity to the study sample. Due to the relatively small number of these highly diverse etiologies, these were discarded from the nTMS and match datasets, resulting in a collective of 127 individual nTMS cases and 379 potential match candidates. This final collective of nTMS patients was then matched

individually to 127 controls. A second matching run was performed in the context of a bootstrap test as outlined in the statistics section.

3.2. Imaging and mapping

Pre- and postoperative MRI scans were performed on a 1.5 T Magnetom Symphony TIM or 3 T Magnetom Skyra (Siemens, Erlangen). For nTMS and intraoperative neuronavigation, a contrast-enhanced T1-weighted axial magnetization-prepared rapid gradient-echo sequence (MPRage) scan was obtained with repetition time TR = 1.9 ms, echo time TE = 3.52 ms, flip-angle 15° and slice thickness of 1 mm. Diffusion weighted imaging (DWI) was acquired for fiber tracking with TR = 5.6 ms, TE = 100 ms, flip-angle 90°, slice spacing 3.6 mm, slice thickness 3 mm.

Navigated transcranial magnetic stimulation was carried out using the Nexstim navigated brain stimulation (NBS) system 4.3 (Nexstim Oy, Helsinki, Finland) according to the currently established protocol by Picht et al. [12-13;36]. Surface electromyography electrodes were attached to the abductor pollicis brevis, first dorsal interosseus, abductor digiti minimi, anterior tibial and/or plantar muscles. The patients were sitting in a reclining chair and asked to relax, keeping their eyes open. First, the resting motor threshold (RMT) was determined by stimulating the presumed localization of the hand knob with varying coil orientation and location. The RMT is defined as the lowest nTMS stimulus intensity in which a 50 µV MEP response (peak-to-peak amplitude) is elicited in five out of ten stimulations. The subsequent mapping then used 110-130% of the RMT and 0.25 Hz, extending over the tumour and adjacent gyri. Coil orientation was perpendicular to the precentral gyrus for the upper extremity and perpendicular to the midline/falx for the lower extremity. However, various angulations were used trying to elicit maximum potentials with each stimulus intensity. MEP amplitudes above 50 µV were considered positive responses and the corresponding stimulation points were marked as motor-eloquent on the MRI (Figure. 3).

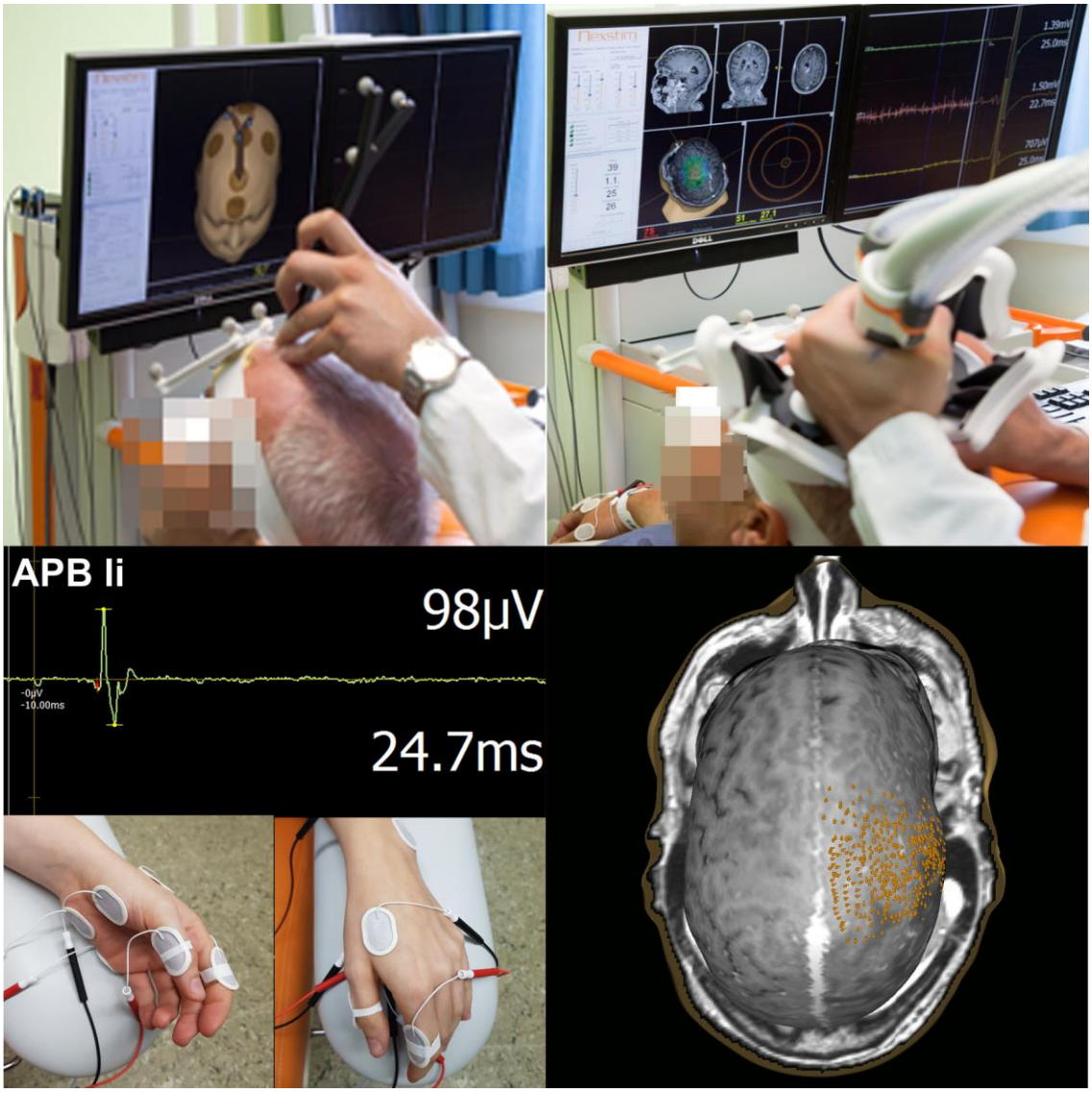


Figure 3. nTMS mapping procedure using the Nextim NBS system. Left upper panel: registration of the individual anatomy of the head surface with the MRI dataset using a marker pen. Right upper panel: stimulation with the coil; the MRI anatomy and the location of the created electric field are shown on the monitors. Lower left: example of the MEP electrodes and response MEP of the abductor pollicis brevis. Lower right: stimulated cortical points for motor mapping.

Fiber tracking of the corticospinal tract was then carried out using the nTMS-based motor cortex as starting region of interest (ROI) in the StealthViz software (Medtronic Inc., Surgical Technologies, Neurosurgery, Coal Creek Circle Louisville, Colorado). A second guidance ROI for the corticospinal tract was placed at the ipsilateral anterior cerebral penduncle. The tracking algorithm used a fractional anisotropy threshold of 0.20, vector step length 1 mm, fibre length of 20 mm minimum, seed density 3.0 and maximum directional change 45° for arm and leg tractography (Figures 4-5) [13].

Surgical resection was carried out under the guidance of MRI-based neuronavigation and intraoperative neuromonitoring by direct cortical stimulation and motor-evoked potentials. In the nTMS group, the nTMS-based motor maps were also included in the intra-operative neuronavigational information. Postoperative adjuvant treatment by radiation and/chemotherapy was administered according to the current guidelines and protocols. Treatment regimens were equal between cases and controls.

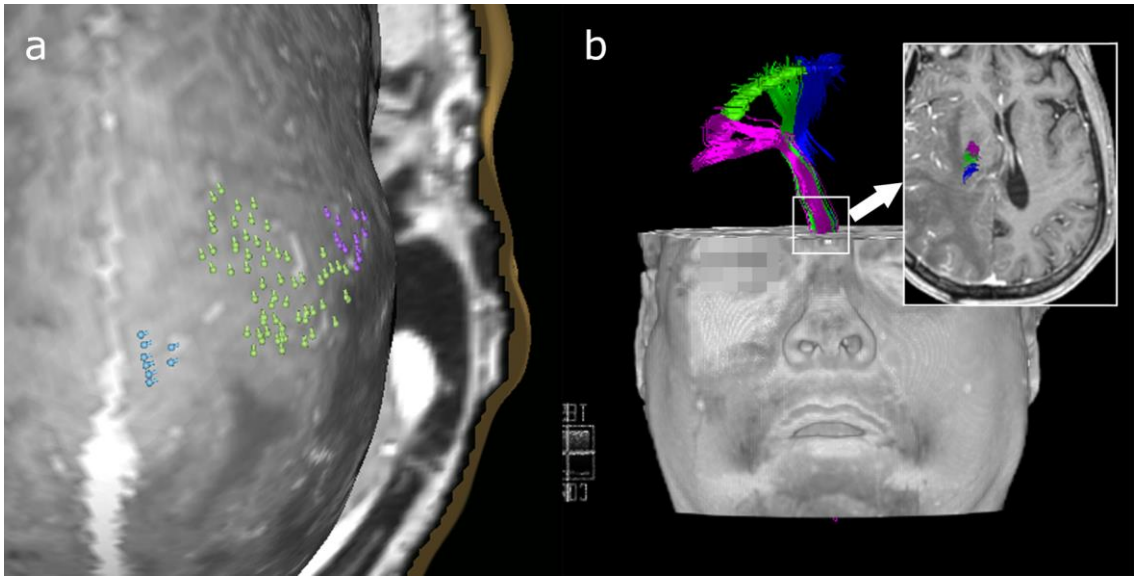


Figure 4. 3D nTMS motor map and fibre tracking. a) motor-eloquent points of the upper (green) and lower (blue) extremity and facial muscles (purple) of the same patient as in figure 3. b) fibre-tracking using these identified motor-eloquent points as seeding points showing the somatotopic organisation of the corticospinal and corticobulbar tracts.

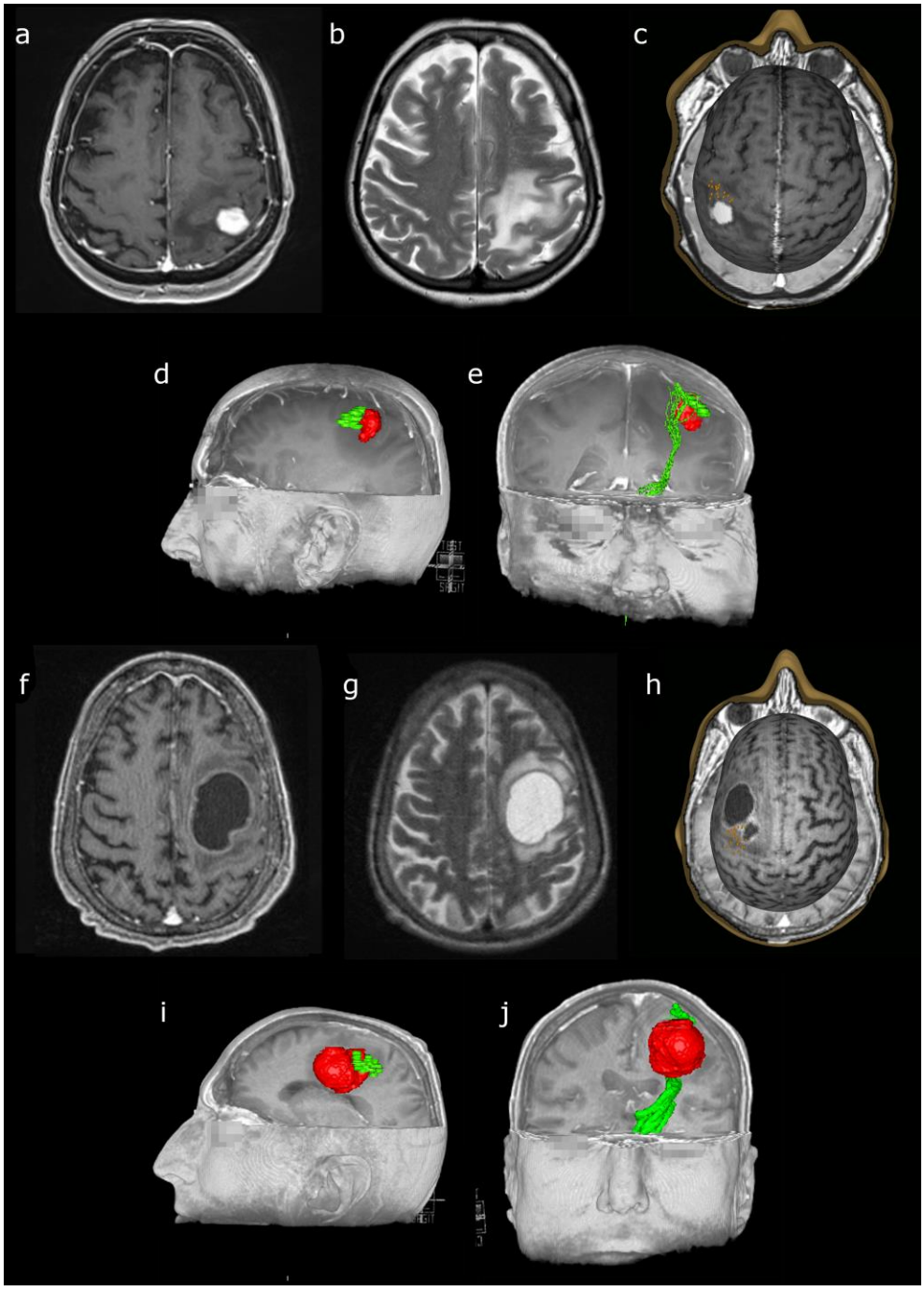


Figure 5. Mapping examples: Female patient (70 years) with a high-grade glioma WHO°III. The patient presented with hemihypesthesia and fine-motor impairment of the right upper extremity. a) contrast-enhanced T1-weighted MRI, b) MRI T2, c) nTMS results of motor-eloquent points in orange. As the projection from the nTMS station is for surgical planning, here the lesion appears to the other side as on the radiological images. d) 3D-projections of tumour volume (red) and motor map (green), e) different projection, together with results from fibre tracking showing the cortico-spinal tract in green. Similarly, case of a 64 year-old male patient with lung cancer metastasis, who presented with a 3/5 paresis. f) T1 with contrast dye, g) MRI T2, h) 3D nTMS motor map, i) 3D segmentation of tumour (red) and motor map (green), j) together with nTMS-based tractography (green fibres).

3.3. Statistics

As the patient collectives were 1:1-matched, pair-wise statistical comparison was carried out using Student's t-test for normally distributed paired data. When a normal distribution could not be presumed, Wilcoxon's signed rank test for paired data was applied. For dichotomous variables and comparison of proportions, McNemar's and McNemar-Bowker's test were used.

After the analysis of the complete matched dataset, several subgroups (metastasis, glioma) were separately analysed. Different subgroups of patient cohorts were compared using the Wilcoxon signed rank test for independent samples.

Binary logistic regression was performed to determine predictors of GTR in gliomas WHO°III/IV. Risk factors associated with reduced overall survival in malignant glioma patients and variables associated with increased resection were assessed by univariate and multivariate Cox regression.

A bootstrap test was included to confirm the validity of the results obtained from the match collective. In the natural sciences, the bootstrap test is commonly applied as a test of the stability and accuracy of observations in a situation when a signal may be obscured by a large amount of noise and the final result is obtained by averaging over a large number of single observations. In medical applications such as in the present study, a bootstrap test can provide confidence that the choice of the match collective – as in this case, the best 1:1 matches as selected out of a collective of potential matches about 3 times the size – will not artificially introduce an effect [7]. Therefore, it was decided to carry out a bootstrap analysis by constructing a second random match collective, in which each nTMS patient was assigned a different match ("bootstrap collective" – BS). This second BS collective was randomly selected out of the remaining possible match candidates omitting the best matches. The same analysis as for the 1:1 matched-pair cohorts was repeated for the BS collective as compared with the nTMS cases (again, 127 BS control patients in a 1:1 matched-pairs analysis vs. the 127 nTMS cases).

The data were collected and prepared in Microsoft Excel. The statistical analysis was carried out in SPSS (version 23 and 25, SPSS inc., Chicago, IL) and OriginPro 2019b (Origin Lab Corporation, Northampton, MA, USA). The level of statistical significance was set to $p < 0.05$.

Figures were created from the PACS surface imported into Microsoft Paint and were modified using the Gnu Image Manipulation Program (GIMP) version 2.10, Microsoft Powerpoint and Photoshop CS5. Treatment plans presented in the outlook section were created in the Philips Pinnacle treatment planning system version 16 (Philips Healthcare, Koniklijke, Netherlands) based on beam data for Siemens Artiste and Siemens Oncor linear accelerators operating at 6 MV photon energies (Siemens Healthcare, Erlangen, Germany).

4. Results

4.1. Preoperative characteristics of the complete dataset

The **demographic** characteristics of the nTMS and control patients (best match as well as bootstrap test) are presented in Table 1. The average patient age (± standard deviation) was 61.0±15.0 years; 58 of 127 patients were female (45.7%). No significant difference is observed in the best match and bootstrap (BS) collectives.

Table 1. Demographic characteristics and preoperative characterization of the collectives.

	nTMS (n=127)	Best match (n=127)	P value	Bootstrap (n=127)	P value
Age [y] (M ± SD)	61.0 ± 15.0	59.6 ± 13.8	0.377	59.6 ± 12.7	0.370
Sex					
Female	58 (45.7%)	44 (34.6%)	0.109	62 (48.2%)	0.615
Male	69 (54.3%)	83 (65.4%)		65 (51.8%)	
Pre-OP motor function					
No paresis	63 (49.6%)	63 (49.6%)	0.760	74 (58.3%)	0.087
Mild paresis	41 (32.3%)	43 (33.9%)		34 (33.9%)	
Severe paresis	23 (18.1%)	21 (16.5%)		19 (16.5%)	
Pre-OP BMRC (M ± SD)	4.2 ± 0.9	4.2 ± 1.0	0.902	4.4 ± 0.8	0.065
Histology					
Glioblastoma	36 (28.3%)	36 (28.3%)		36 (28.3%)	
HGG WHO III	11 (8.7%)	11 (8.7%)		11 (8.7%)	
LGG WHO II	5 (3.9%)	5 (3.9%)	1.000	5 (3.9%)	1.000
Metastases	53 (41.7%)	53 (41.7%)		53 (41.7%)	
Meningioma	16 (12.6%)	16 (12.6%)		16 (12.6%)	
Cav. Malform.	6 (4.7%)	6 (4.7%)		6 (4.7%)	
Location					
Frontal	88 (69.3%)	88 (69.3%)	1.000	81 (63.8%)	0.351
Parietal	39 (30.7%)	39 (30.7%)		46 (36.2%)	
Lesion diameter [cm]	2.6 ± 1.2	2.6 ± 1.2	0.678	2.7 ± 1.2	0.451
Lesion volume [cm³]	14.5 ± 17.1	15.3 ± 18.0	0.632	15.0 ± 17.2	0.773

Most **lesions** in the data set were metastases (42%), followed by glioblastoma multiforme (GBM, WHO°IV, 28%). All glioma (GBM, HGG=high grade glioma WHO°III and LGG=low grade glioma WHO°II) together made up 41% of the cases. 12% of the lesions were meningioma, only 5% cavernoma (Figure 6). 100 patients (78.7%) suffered from primary or secondary malignant intra-axial lesions (glioma WHO°III-IV or metastasis). As the etiology was congruently matched (no cross-assignments), the same distribution applies to the match and bootstrap collectives (p = 1.0).

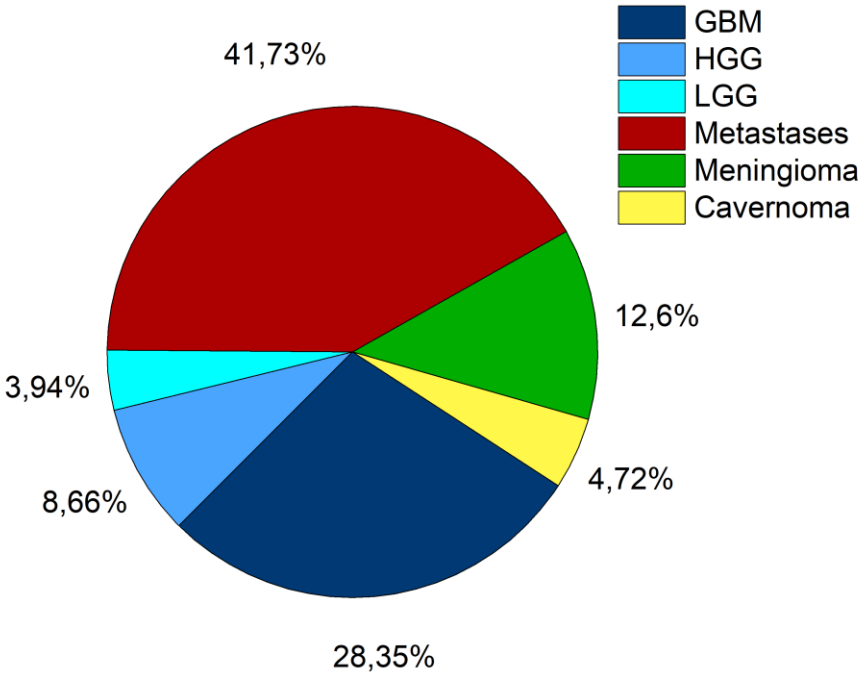


Figure 6. Lesion etiology of the patient collective. GBM = glioblastoma multiforme WHO°IV, HGG = high grade glioma WHO°III, LGG = low grade glioma WHO°II.

For most lesions (88/127 = 69.3%), lesion bulk was **located** frontal to the central sulcus, which is explained by the inclusion criteria of motor-eloquent lesions in this collective. Any lesion situated within the precentral gyrus would be considered motor-eloquent and hence included in the dataset. Lesions located more parietally would only be considered if they infiltrated the motor cortex or created sufficient mass effect to compress the central sulcus and precentral gyrus (as described in 3.1.1). In the best match dataset, frontal lesions were always assigned frontal match partners, and

parietal lesions parietal matches, so that there is ideal correspondence between these two collectives (p = 1.0). For the BS cohort, this could not be held (only 81 frontal lesions), but the difference in proportion is statistically insignificant (p = 0.351).

The average **lesion diameter** was 2.6±1.2 cm (for nTMS and best match) and 2.7±1.2 cm for BS (no significant difference) and estimated **lesion volume** 14.5±17.1 cm^3 vs. 15.3±18.0 cm^3 (not significant (n.s.)) for nTMS vs. best match and 15.0±17.2 cm^3 (n.s.) for BS, respectively. An overview of the distribution of these parameters as well as BMRC ranks is given in the Appendix.

Preoperative motor function was unimpaired in about half of the nTMS-patients (63 patients without paresis, 49.6%). 32.3% (41 patients) presented with mild paresis and 18.1% (23 patients) with severe paresis. These proportions were similar in the match cohort (49.6%, 33.9% and 16.5%, respectively, p=0.760). The BS cohort could not be matched as closely and presented with a trend towards better preoperative motor-function (74/127 = 58.3% without paresis), without reaching statistical significance (p=0.087). A similar tendency is observed in the average preoperative BMRC rank (4.2 for the nTMS and best match collectives vs. 4.4 ± 0.8 for the BS collective, n.s.).

4.2. Outcome in nTMS vs. non-nTMS patients

The functional and surgical outcomes of the nTMS and match cohorts are displayed in Table 2. In the nTMS cohort, 10 patients (7.9%) suffered from permanent and 5 patients (3.9%) from transient **surgery-related paresis** (Figure 7), compared with 9 (7.1%) and 5 (3.9%) in the match collective and 8 (6.3%) and 7 patients (5.5%) in the bootstrap collective (n.s.).

Considering **change in motor function** during follow-up in comparison with the preoperative performance (Figure 8), improvement was observed in 49/127 (38.6%) of nTMS patients and 51/127 (40.2%) of best matches, about half of the patients remained unchanged (68/127 nTMS and 67/127 best match) and a small proportion deteriorated (10/127 = 7.9% of nTMS and 9/127 = 7.1% best matches), with no significant difference between the nTMS and control group.

Table 2. Postoperative outcome at discharge (average day 7) and follow-up (average day 60): motor function, extent of resection, craniotomy size, duration of surgery and hospital stay. P-values < 0.05 (statistically significant) are highlighted in bold type.

	nTMS (n=127)	Best match (n=127)	P value	Bootstrap (n=127)	P value
BMRC rank day 7	4.2 ± 1.0	4.3 ± 1.1	0.534	4.4 ± 1.1	0.277
BMRC rank day 60	4.6 ± 1.0	4.6 ± 1.0	0.603	4.7 ± 0.7	0.264
Surgery-related paresis None Transient Permanent	 112 (88.2%) 5 (3.9%) 10 (7.9%)	 113 (89.0%) 5 (3.9%) 9 (7.1%)	0.996	 112 (88.2%) 7 (5.5%) 8 (6.3%)	0.757
motor outcome at day 60 Improved Unchanged Deteriorated	 49 (38.6%) 68 (53.5%) 10 (7.9%)	 51 (40.2%) 67 (52.8%) 9 (7.1%)	0.344	 40 (31.5%) 79 (64.2%) 9 (7.1%)	0.303
Gross total resection	107 (84.3%)	93 (73.2%)	**0.020**	85 (68.5%)	**0.003**
Craniotomy diameter [cm]	4.4 ± 1.1	4.6 ± 1.2	0.072	4.9 ± 1.5	**0.002**
Duration of surgery [mins]	115 ± 56	126 ± 58	0.124	119 ± 56	0.595
Hospital stay [days]	9.0 ± 4.7	8.9 ± 5.8	0.878	9.0 ± 4.5	0.938

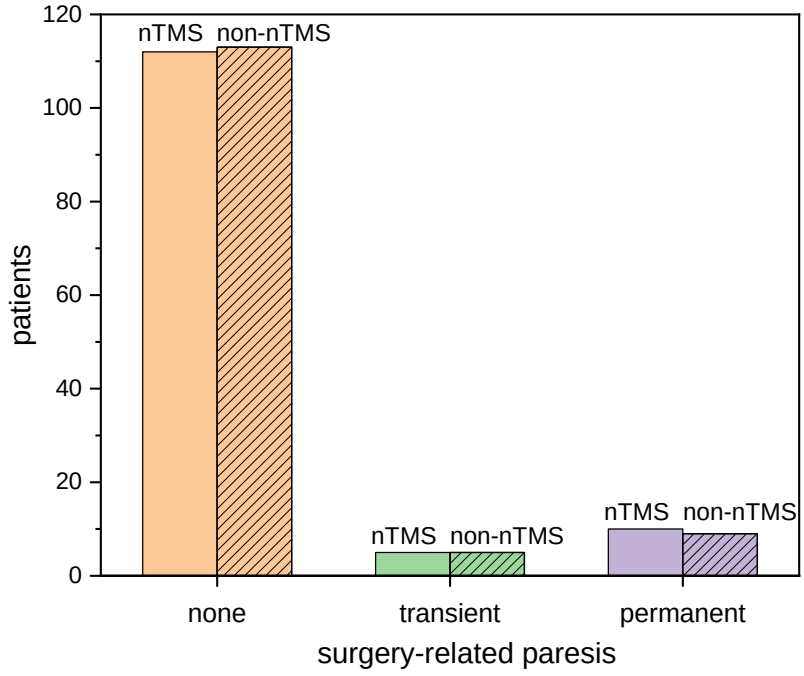


Figure 7. Surgery-related paresis (transient or permanent) for nTMS patients and best matches. There are no significant differences between nTMS and non-nTMS group. This result is confirmed by the bootstrap analysis (not shown in the figure).

When interpreting the seemingly low proportion of patients with improved motor function, it must be kept in mind that 63 patients (49.6%) did not exhibit preoperative motor impairment (so improvement was not possible). Considering only the collective of patients with paresis (64/127), the number of 49 patients with improved motor performance corresponds to a proportion of 76.6%.

Looking at the bootstrap collective, the proportions of patients with unchanged, improved and deteriorated motor function appear quite different, with a higher number of patients exhibiting no change in function (79/127 = 64.2%) and a smaller number showing improved motor outcome (40/127 = 31.5%). Again, these relative numbers are biased by the preoperative better functional status of the bootstrap collective. As a larger number of BS patients presented without preoperative paresis (74 vs. 63 in the nTMS collective), these patients did not offer room for improvement, resulting in a larger number of patients without change in motor function. If the number of patients with improved motor performance is scaled in proportion to the number of patients with preoperative paresis (64 in nTMS collective and 53 in BS), an improvement is seen in 49/64 = 76.6% of nTMS patients and in 40/53 = 75.5% of BS patients, yielding no significant difference.

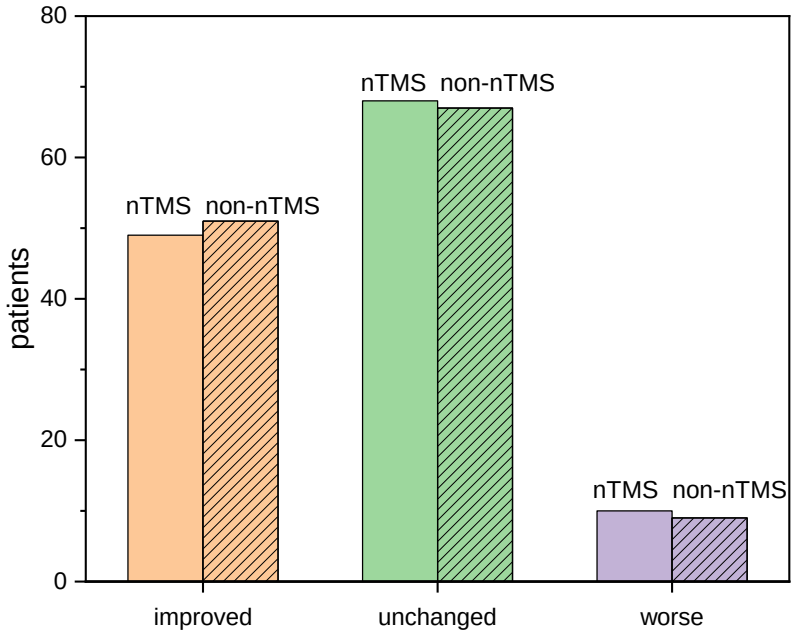


Figure 8. Change in motor function during follow-up (day 60) as compared with preoperative status. Again, no significant difference is observed between nTMS and non-nTMS groups.

This result is confirmed by considering pre- vs. postoperative **BMRC rank**. While no significant difference is observed directly postoperatively in the nTMS collective, the average rank during follow-up is significantly improved over the preoperative status (4.6 vs. 4.2, p = 0.003). The same holds for the match and BS group.

Considering the surgical endpoints, a significant difference between nTMS and match group was observed in the rate of gross total resection. GTR was achieved in 107 patients (84%) in the nTMS group vs. 93 patients (73.2%) in the control group (p = 0.020), while maintaining equal motor performance between both groups. This result was confirmed by the bootstrap test.

No significant differences were observed between the three collectives regarding **duration of surgery** (115±56 min in nTMS) and **duration of hospital stay** (9.0±4.7 days in nTMS group). In **craniotomy size**, there was a trend towards smaller craniotomy diameter in the nTMS group (4.4±1.1 cm vs. 4.6±1.2 cm in the best match group, p=0.072), which only reached statistical significance in the BS group (4.9±1.5 cm, p=0.002). As the best match and BS control group differ in craniotomy size, it remains unclear if this effect is realistic or caused by selecting the match collectives.

The analysis was repeated for the following reduced data collectives:

- the dataset of intra-axial lesions (111 patients), i.e. excluding meningioma
- the dataset of only intra-axial brain tumours (105 patients), i.e. excluding meningioma and cavernoma
- the dataset of only intra-axial malignant tumours (100 patients), i.e. excluding meningioma, cavernoma and low-grade glioma
- the dataset of only meningioma patients (16 patients)
- the dataset of only cavernoma patients (6 patients).

The results of these slightly reduced subgroups confirm the results for the complete collective presented above; the corresponding tables are shown in the Appendix. For the more homogeneous subgroups of patients with metastases and patients with malignant glioma, the results are presented in the following section.

4.3. Subgroup analysis of patients with metastases

The 53 patients with metastases were separately analysed (Table 3). In comparison to the complete collective, there was a larger proportion of patients without preoperative paresis, and the lesion diameter and volume were smaller.

Table 3. Demographic characteristics and outcome of patients with metastases.

	nTMS (n=53)	Best match (n=53)	P value
Age [y] (M ± SD)	64.4 ± 12.2	64.4 ± 11	0.982
Sex			
Female	25 (47.2%)	18 (34.0%)	0.281
Male	28 (52.8%)	35 (66.0%)	
Pre-OP motor fct			
No paresis	21 (39.6%)	23 (43.4%)	0.223
Mild paresis	20 (37.7%)	16 (30.2%)	
Severe paresis	12 (22.7%)	14 (26.4%)	
Preoperative BMRC (M ± SD)	4.1 ± 0.9	4.0 ± 1.1	0.168
Location			
Frontal	38 (71.7%)	38 (71.7%)	1.000
Parietal	15 (28.3%)	15 (28.3%)	
Lesion diameter [cm]	2.2 ± 1.0	2.2 ± 1.0	0.568
Lesion volume [cm³]	8.7 ± 12.4	8.9 ± 10.6	0.903
BMRC day 7	4.3 ± 0.8	4.2 ± 1.2	0.583
BMRC day 60	4.7 ± 0.8	4.4 ± 1.1	0.182
Surgery-related paresis			
None	52 (98.1%)	49 (92.5%)	n/c
Transient	0 (0.0%)	1 (1.9%)	
Permanent	1 (1.9%)	3 (5.7%)	
motor outcome at day 60			
Improved	28 (52.8%)	26 (49.1%)	0.368
Unchanged	24 (45.3%)	24 (45.3%)	
Deteriorated	1 (1.9%)	3 (5.7%)	
Gross total resection	48 (90.6%)	46 (86.8%)	0.727
Craniotomy diameter [cm]	3.9 ± 0.8	4.1 ± 0.9	0.088
Duration of surgery [mins]	90 ± 34	103 ± 52	0.123
Hospital stay [days]	8.6 ± 3.9	9.5 ± 7.6	0.458

n/c: not calculated because of zero value in table (transient paresis).

In the metastasis group, the vast majority of patients (98.1% in the nTMS group, 92.5% in the control group) did not experience any surgery-related paresis. While there appeared to be a tendency to fewer surgery-related deficits in the nTMS group, the statistical difference could not be proven by the McNemar-Bowker's test because the number of patients with transient or permanent paresis was so small (only one patient with paresis in the nTMS group, 1.9%). Similarly, only one nTMS-patient with metastasis experienced a deterioration in postoperative motor function during follow-up, about half (28/53 = 52.8%) improved, the others (24/53 = 45.3%) remained unchanged, with no statistically significant difference as compared with the best match group (49.1% improved, 45.3% unchanged, 5.7% deteriorated, $p = 0.368$). As only 32/53 patients (60.4%) had preoperative paresis in this group, this indicates that nearly all patients with metastases recovered completely, and indeed all except for 10 patients presented with full strength at follow-up. This is also reflected in the BMRC rank of 4.7 ± 0.8, which is significantly higher than preoperatively (4.1 ± 0.9, $p < 0.001$), but without statistically significant difference between nTMS and control patients.

In contrast to the results for the complete collective, no significant difference between gross total resection rates could be found for the patients with metastases (48/53=90.6% nTMS vs. 46/53=86.6% controls, p=0.727). Secondary surgical outcome parameters such as duration of surgery and craniotomy size also did not yield any statistical difference between the nTMS and control group.

4.4. Subgroup analysis of patients with malignant gliomas

As a second subgroup, patients with malignant glioma, i.e. glioblastoma multiforme WHO°IV and high-grade glioma WHO°III were analysed as composite, as shown in Table 4. There were 47 patients in this collective, 36 (76.6%) with GBM WHO°IV and 11 (23.4%) with WHO°III (identically in the nTMS group, best match control group and bootstrap group, p = 1.000).

Table 4. Demographic characteristics & outcome of patients with malignant glioma WHO°III-IV.

	nTMS (n=53)	Best match (n=53)	P value
Age [y] (M ± SD)	62.4 ± 15.2	58.1 ± 12.1	0.120
Sex			
Female	18 (38.3%)	16 (34.0%)	0.832
Male	29 (61.7%)	31 (66.0%)	
Pre-OP motor fct			
No paresis	22 (46.8%)	21 (44.7%)	0.549
Mild paresis	17 (36.2%)	21 (44.7%)	
Severe paresis	8 (17.0%)	5 (10.6%)	
Preoperative BMRC (M ± SD)	4.2 ± 1.0	4.3 ± 0.9	0.543
Location			
Frontal	33 (70.2%)	33 (77.2%)	1.000
Parietal	14 (29.8%)	14 (29.8%)	
Lesion diameter [cm]	3.0 ± 1.0	3.1 ± 1.2	0.625
Lesion volume [cm³]	18.3 ±16.8	21.8 ± 21.3	0.201
BMRC day 7	4.1 ± 1.2	4.1 ± 1.3	0.726
BMRC day 60	4.4 ± 1.2	4.5 ± 1.2	0.923
Surgery-related paresis			
None	39 (83.0%)	41 (87.2%)	0.919
Transient	2 (4.3%)	2 (4.3%)	
Permanent	6 (12.8%)	4 (8.5%)	
motor outcome at day 60			
Improved	14 (29.8%)	17 (36.2%)	0.521
Unchanged	27 (57.4%)	26 (55.3%)	
Deteriorated	6 (12.8%)	4 (8.5%)	
Gross total resection	34 (72.3%)	25 (53.2%)	**0.049**
Craniotomy diameter [cm]	4.8 ± 1.2	5.0 ± 1.2	0.296
Duration of surgery [mins]	126 ± 56	139 ± 50.0	0.242
Hospital stay [days]	10.1 ± 5.8	8.8 ± 4.8	0.221

Postoperative motor outcome was again unchanged in slightly more than half of the patients (27/47 = 57.4% in the nTMS group, 26/47 = 55.3% best match group, n.s.), however, compared with the metastasis collective, a larger proportion of patients deteriorated postoperatively (6/47 = 12.8% nTMS and 4/47 = 8.5% best matches), with no significant differences between nTMS and non-nTMS groups.

Similarly, to the analysis for the complete collective, again a significant difference in gross total resection rates was observed between the nTMS (34/47 = 72.3%) and non-nTMS collectives (25/47 = 53.2%, p = 0.049), while preserving functional outcome. None of the other outcome parameters differed significantly between these groups.

GTR rates for the complete collective and several sub-groups are displayed in Figure 9. Evidently, all subgroups of glioma patients (WHO°II-IV, WHO°III-IV and only WHO°IV) exhibited a significant difference in GTR between the nTMS and control group, without differences in motor function.

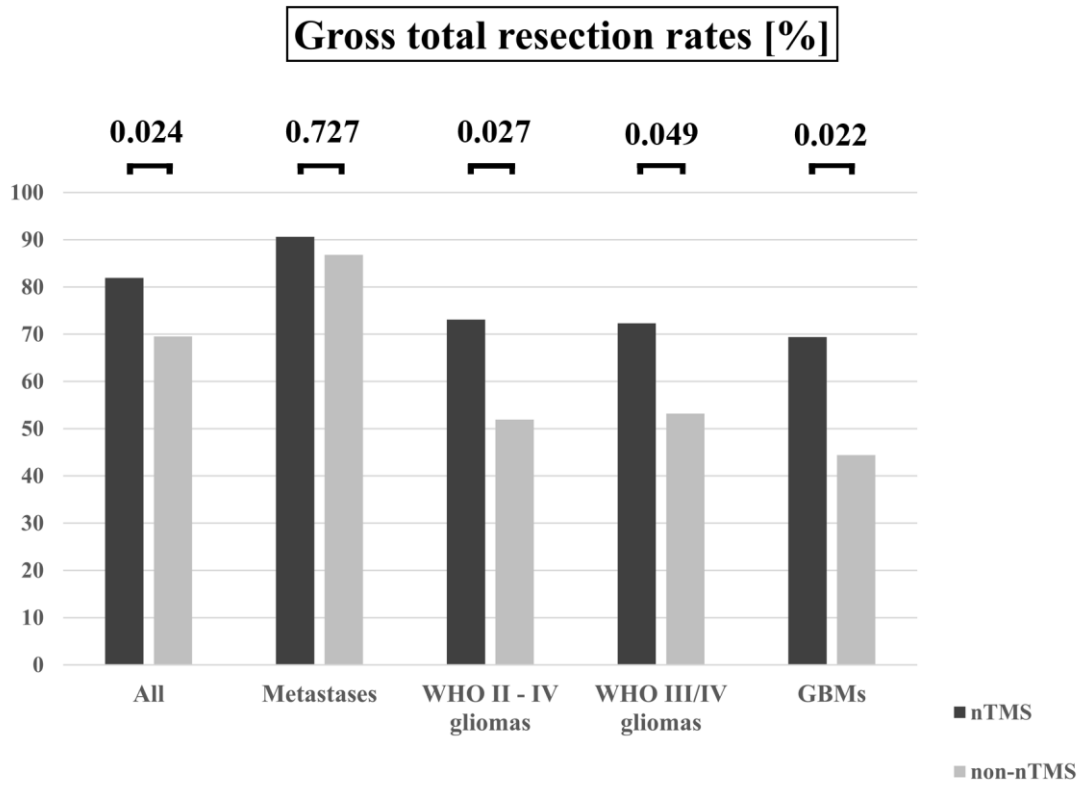


Figure 9. Comparison of gross total resection rates (in %) for nTMS group and best match.

To verify the observed change in gross total resection with preserved motor function for nTMS patients with malignant glioma WHO°III/IV, a multivariate analysis was carried out to find variables significantly associated with improved gross total resection (Table 5).

Table 5. Predictors of gross total resection (GTR) among malignant glioma WHO°III-IV in multivariable logistic regression. OR = odds ratio, CI = confidence interval.

	OR (95% CI)	P value
nTMS motor mapping	2.625 (1.035 – 6.659)	0.042
Tumour diameter	0.954 (0.915 – 0.995)	0.030
Preoperative motor status quantified by BMRC	1.759 (1.021 – 3.032)	0.042

Multivariate analysis shows that preoperative nTMS motor mapping is an independent predictor for achieving gross total resection (odds ratio OR = 2.625, 95% confidence intervals (CI) 1.035-6.659, p = 0.042). GTR is also more frequently achieved for smaller tumour diameter (p = 0.030) and better preoperative motor status as quantified by BMRC rank (p = 0.042).

Due to the difference in GTR between nTMS and non-nTMS patients with malignant glioma, it was decided to test whether this difference results in increased overall survival of these patients. This analysis is presented in the next section.

4.5. Survival analysis for malignant glioma patients

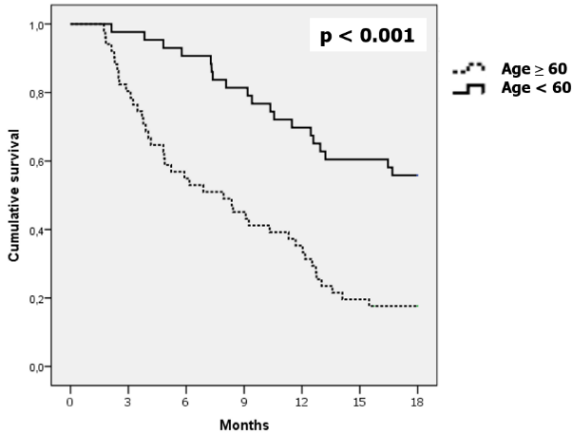
Univariate survival analysis of the patients in the malignant glioma (WHO°III/IV) subgroup shows significantly increased overall survival with younger patient age (< 60 years, $p < 0.001$), unimpaired preoperative functional status (no preoperative paresis, $p = 0.001$), and after undergoing gross total resection ($p = 0.016$) (Figure 10). However, no significant influence of preoperative nTMS mapping could be discerned ($p = 0.123$).

In multivariate Cox-regression analysis (Table 6), only age (quantitative variable) and tumour residual (dichotomous variable) remained significantly associated with poorer 18-months survival, with older age presenting with an odds ratio of OR = 1.045 ($p < 0.001$) and tumour residual with OR = 1.877 (95% confidence intervals 1.075-3.279, $p = 0.027$). There was a trend towards reduced survival with preoperative paresis (OR = 1.657), however, statistical significance was not reached in the multivariate analysis ($p = 0.084$).

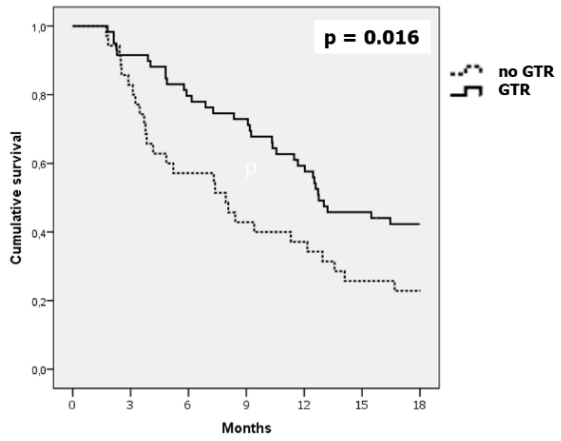
Table 6. Results of multivariate Cox-regression analysis for overall survival of patients with malignant glioma. OR = odds ratio, CI = confidence interval

	OR (95% CI)	P value
Older age	1.045 (1.023 – 1.067)	< 0.001
Tumour residual	1.877 (1.075 – 3.279)	0.027
Preoperative paresis	1.657 (0.935 – 2.935)	0.084

Age ≥ 60



Gross total resection



Preoperative paresis

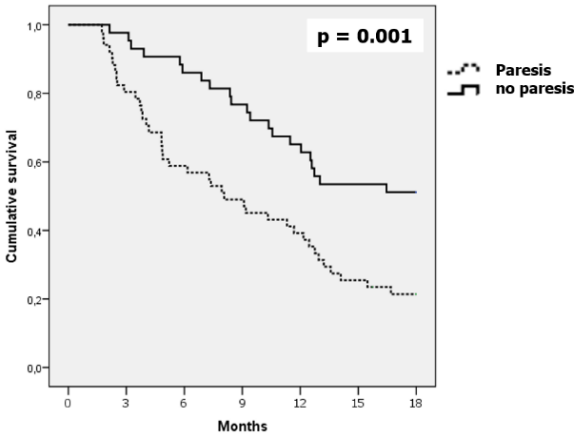


Figure 10. Univariate survival analysis for patients with malignant glioma WHO°III-IV.

To assess for treatment bias regarding differing adjuvant treatment regimes, medical records were revised to obtain information on chemotherapy and radiotherapy of the malignant glioma collective (Table 7). The majority of patients were treated according to the Stupp protocol [55] using combined radiotherapy with 60 Gy in daily fractions of 2 Gy (5 days per week over 6 weeks) and concomitant chemotherapy with temozolomide, followed by adjuvant temozolomide chemotherapy. Reasons to deviate from this protocol included poor general condition and palliative management, severe thrombopenia or renal failure resulting in interruption or break-off of chemotherapy, claustrophobia preventing radiotherapy, or lack of informed consent. Treatment regimens were in accordance with current guidelinines and protocols. For patients presenting with relapse/recurrence, (10 nTMS cases, 13 controls, n.s.), different approaches were individually chosen. The comparison of therapeutic regimes did not show any statistically significant difference between the nTMS and control groups, so that there is no indication for treatment-associated bias in the survival analysis.

Table 7. Adjuvant therapy regimes of patients with malignant glioma WHO°III-IV.

	nTMS	Controls	P value
Relapse/recurrence	10	13	n.s.
Combined radiation and chemotherapy	21	28	n.s.
Chemotherapy only	9	10	n.s.
Radiotherapy only	9	6	n.s.

5. Discussion & Outlook

5.1. Comparison with previous studies

The value of preoperative nTMS mapping of the motor cortex to guide surgical resection was first presented for a small collective of 11 patients with low-grade gliomas by Picht et al. [37], compared to 11 historical control patients. Although the study collective was too small to allow for rigorous statistical evaluation, the authors could show that the addition of nTMS information influenced clinical decision-making for these patients. More patients received surgical treatment rather than watchful waiting and surgery aimed for more extensive resection in the nTMS group compared to controls. Postoperative pathology revealed that 4 out of 10 nTMS patients with presumed low-grade glioma turned out to already exhibit histological features compatible with glioma WHO°III. No significant difference in functional outcome was observed in the nTMS vs. non-nTMS group. This paper provided first indication that the addition of nTMS could improve the clinical management of glioma patients, as it may support a more aggressive surgical strategy.

Table 8 a-c gives an overview of the subsequent studies regarding nTMS mapping of the motor cortex for various lesion etiologies, and for metastases and gliomas separately. The largest landmark studies are presented in more detail below.

5.1.1. Studies regarding various entities

The first extensive matched-cohort studies on the clinical impact of preoperative nTMS mapping of the motor cortex for the resection of tumours located in the vicinity of the central region were presented by Krieg et al. [20] and Frey et al. [8]. In the former study, 100 consecutive patients with motor eloquent brain lesions (astrocytoma WHO°II/III, GBM, metastasis, arterio-venous malformations, cavernoma and others) received preoperative nTMS mapping of the motor cortex. These were matched to a

historical cohort of 100 patients (whether 1:1 or group-wise was unspecified). General motor outcome was better in the nTMS cohort, with improved function observed in 12 out of 34 patients with preoperative paresis (35.3%), but only in 1/27 (3.7%) of control patients with paresis ($p = 0.0057$). Furthermore, a lower proportion of the nTMS patients (22%) exhibited residual tumour on postoperative MRI, significantly less than in the control cohort with 42% (OR 0.3828; CI 0.2062-0.7107). Secondary surgical outcome variables such as surgery-related paresis and duration of surgery showed no significant difference between the collectives; however, craniotomy size was significantly reduced in the nTMS group.

Frey et al. [8] compared an nTMS cohort of 250 patients (128 glioma WHO°II-IV, 85 metastases, 37 others) with 115 non-nTMS patients. However, a detailed analysis was performed only only for the subgroup of glioma patients, which will be discussed in section 5.1.3. For the complete collective (all histologies), they observed no significant difference in postoperative motor performance.

This thesis confirms the above reported increased gross total resection rates, without significant change in motor outcome. The number of patients with improved motor function during follow-up is of the same order of magnitude as in previous reports (38.6% in this thesis vs. 35.3% [20] and 32.7% [12]). Permanent and transient surgery-related paresis occurred rarely (7.9% and 3.9% in this thesis vs. 13% and 16% [20], 17.4% and 4.7% [53]).

Similar to Frey et al. [8] but different from Krieg et al. [20], the present study could not show improved motor function in the nTMS collective compared to controls. This does not indicate worse outcome the nTMS collective, but rather an overall improved motor outcome in the control group: in the study by Krieg et al. [20], very few patients in the control group showed improved motor function (3.7% vs. 35.3% in the nTMS group), whereas this thesis finds improved motor performance in 38.6% of control and 40.2% of nTMS patients (n.s.). There may be a number of reasons contributing to this difference: firstly, the study by Krieg et al. [20] did show some differences in preoperative motor function between the nTMS and non-nTMS group, although this did not reach statistical significance (66% of nTMS patients without preoperative paresis vs. 73% non-nTMS; 24% of nTMS patients with mild preoperative paresis vs. 15% non-nTMS). Secondly, there may differences in surgical practice between the centres, or improved resection and preservation of motor status over the past years. This

hypothesis is strengthened by the proportion of patients for whom GTR could not be achieved: 22%/42% for nTMS/controls in [20], and only 15.7%/26.3% in this thesis.

5.1.2. Metastases

With a focus on metastases (Table 8b), the first study was published in 2016 by Krieg et al. [22], who matched 120 nTMS patients to 130 control patients. The authors confirmed their previous results for mixed histologies [20] in that a larger proportion of nTMS patients with preoperative paresis improved during follow up (37/62 = 59.7%) than of the control patients (17/51 = 33.3%; p = 0.0002). Furthermore, a smaller number experienced new permanent surgery-related paresis (4/120 = 3.3% in nTMS vs. 17/130=13.1% in the non-TMS group, p = 0.016). Again, however, there was a marked difference between preoperative motor function in the nTMS and non-nTMS group, though without reaching statistical significance (no preoperative paresis in 48.3% vs. 60.8% of nTMS vs. controls; mild paresis in 33.3% vs. 26.9%, respectively). Extension of craniotomy in anterior-posterior and lateral directions and duration of surgery were significantly reduced by nTMS, and a much smaller fraction of patients exhibited residual tumour in the nTMS group (7.7% vs. 21.6%, p = 0.0024) [22].

Again, this thesis has found no significant difference in motor outcome between the nTMS and control groups. This difference arises because the control group exhibits a better outcome in the present collective. Therefore, both nTMS and non-nTMS groups achieve similar results as the nTMS group in Krieg et al. [22]. A tendency may be present here towards better outcome in the nTMS patients, but this does not reach statistical significance (improved in 52.8% of nTMS patients and 49.1% of control patients, n.s.). Similarly, the present thesis observed a lower frequency of surgery-related deficits than Krieg et al. [22] both for the nTMS and match cohorts: in the nTMS group, only one patient with permanent surgery-related paresis (1.9% vs. 3.3% [22]), and three patients (5.7%) in the control group (13.1% [22]). In general, metastases are better demarcated from the brain parenchyma than gliomas and therefore more prone to be resected gross total without functional deficits. However, a comparison of the present thesis with the results by Krieg et al. [22] is hampered as the proportion of possibly mucinous and less easily demarcated histologies in the metastasis collectives may differ.

5.1.3. Malignant glioma WHO°III/IV

Considering malignant glioma patients only, Krieg et al. [21] observed a trend towards improved postoperative motor function in nTMS patients (more patients with improved and less patients with deteriorated function), without attaining statistical significance. Duration of inpatient stay was reduced in the nTMS patients (median 12.0 vs 14.0, $p = 0.0446$) and overall craniotomy area was also significantly reduced in the nTMS collective (25.3 ± 9.7 cm² vs. 30.8 ± 13.2 cm², $p = 0.0058$). A lower rate of nTMS patients with postoperative residual tumour was confirmed for this collective as well (34.3% vs. 54.3%, $p = 0.0172$), which translated into increased overall survival of nTMS patients with glioma WHO°III ($p = 0.0322$). For WHO°IV glioblastoma multiforme, a statistically significant difference was seen only at specific time-points during follow-up (3-6 months, but not for overall survival and 12 months). However, these results should be interpreted with caution, since there was a significant difference in the percentage of patients receiving adjuvant radiotherapy in the nTMS and non-nTMS groups ($p = 0.0261$), which might have contributed a greater effect than nTMS mapping [21].

In their subgroup analysis of patients with glioma, Frey et al. [8] confirmed increased GTR rates (58.6% nTMS vs. 42.8% non-nTMS, $p < 0.05$) without difference in motor outcome. No difference in overall survival was observed for this cohort. Progression-free survival was not observed to be different for the complete collective of WHO°II-IV gliomas, but improved for the LGG gliomas WHO°II (median 22.4 vs. 15.4 months, $p < 0.05$). However, this result relied on only 38 nTMS and 18 non-nTMS patients, and no information is available on the matching for this subgroup.

A first controlled observational study was carried out by Picht et al. [39] comparing patients with motor-eloquent glioblastoma treated at two campuses of the same university hospital, only one of which was equipped with nTMS (93 nTMS patients and 34 controls with intra-operative DCS only). Both study arms presented homogeneous patient characteristics with respect to tumour location, tumour volume, age, sex, and preoperative motor status. No significant difference in postoperative motor performance was seen, the only difference arising in the occurrence of transient surgery-related deficit (24 patients = 26% in the nTMS arm vs. 1 case = 3% in the non-nTMS arm, $p = 0.0076$). In permanent deficit, no significant difference was observed

(13% and 15%, respectively). The extent of resection was better in the nTMS group (gross total resection 61% vs. 45% in the control group, p = 0.012.

Interestingly, the results for glioma that were obtained in the present thesis (improvement in 29.8% of patients, deterioration in 12.8%) appear considerable more favourable than earlier studies (vs. 4.3%/5.7% improvement/deterioration [21]; 18.6%/15.0% [44], 9%/9.1% [39]/[37]). However, these studies included different proportions of patients with glioma WHO°II, III and IV, which may bias the comparison. Regarding surgery-related paresis (transient/permanent), the observations agree well with each other (present thesis 4.3%/12.8% vs. 8.6%/12.9% [21], slightly worse outcomes in [39] 26%/13% and 4.3%/20.3% [53]).

Comparing the present gross total resection rates to Krieg et al. [21] and Picht et al. [39], the patients in this thesis more frequently achieved GTR (72.3%/53.2% in this thesis vs. 65.7%/46.7% [21] and 61%/45% [39]), always with a significant improvement for the nTMS collective. Taken together, only one study [21] could show a significant association with overall survival, which may have been influenced by different adjuvant radiotherapy regimes.

In conclusion, this thesis can confirm the previous results in that nTMS can lead to increased gross tumour resection in the subgroup of glioma patients, while at least maintaining motor outcome. It might even be improved as reported by others [21].

Table 8 (next pages). Overview of previous nTMS studies and results from the present thesis. a) collectives with mixed entities; b) metastases; c) gliomas. n.s. = not significant; SRP = surgery-related paresis, OS = overall survival, PFS = progression free survival, DS = duration of surgery, HS = duration of hospital stay. Significant results are marked in blue font.

Table 8. Overview of previous nTMS studies and results from the present thesis. a) collectives with mixed lesion entities
n.s. = not significant, SRP = surgery-related paresis, OS = overall survival, PFS = progression-free survival, DS = duration of surgery, HS = hospital stay. Significant differences are marked in blue font

Reference	nTMS/ controls	Motor outcome in nTMS/control	Resection outcome in nTMS/control	Survival	Craniotomy size	Duration of surgery/ Hospital stay	comments
Krieg et al. (2014) [20]	100/100 (group- or pair-wise)	Improved 35.3%/3.7%, SRP transient 16% permanent 13% (n.s.)	GTR 78%/58%	Not assessed	AP 4.9±0.9/ 5.4±1.5 cm; area 22.4±8.3/ 26.7±11.3 cm²	DS 196.2±57.5 min (n.s.) HS not assessed	*Pre-operative paresis not well matched*
Frey et al. (2014) [8]	250/115 (group-wise)	BMRC 3 months post-OP 4.3/4.0 (n.s.)	Assessed only for glioma – see table 9 c	Assessed only for glioma – see table 9 c	Not assessed	Not assessed	
Hendrix et al. (2016) [12]	61 – no controls	Improved 32.7%, none worse; transient deterioration in 18.0%	GTR 86.9 %	Not assessed	Not assessed	Not assessed	Sub-collective of the patients from this thesis
Sollmann et al. (2018) [53]	116 – no controls	SRP permanent 17.4 %; transient 4.7% (n.s.)	Not assessed	Not assessed	Not assessed	Not assessed	Correlation of outcome with distance of lesion from motor-eloquent area
This thesis	127/127 (1:1 paired with BS test)	improved in 38.6%, deteriorated in 7.9%; SRP permanent 7.9%; Transient 3.9% (n.s.)	GTR 84.3%/73.7%	Not assessed for entire collective, see metastases and glioma separately	diameter 4.4±1.1 cm (n.s.)	ST 115±56 min; HS 9.0±4.7 days (n.s.)	

Table 8 b (continued) – Metastases

Reference	Patients	Motor outcome	Resection	Survival	Craniotomy size	DS/HS	comments
Krieg et al. (2016) [22]	120/130	Improved: 59.7%/33.3%; SRP permanent 3.3%/13.1%; SRP transient 2.5% (n.s.)	GTR 92.3%/78.4%	Not assessed	AP 5.0±1.6/ 6.1±2.1 cm; Lat 3.4±1.3/ 4.0±1.9 cm; Area 16.7±8.6/ 25.0±17.1 cm²	DS 128.8±49.4/ 158.0±65.8 min	
Hendrix et al. (2016) [12]	23 – no controls	Improvement in follow-up: 85.7 % of patients with paresis, 56.7 % overall patients; Deterioration 4.3%	Total resection in 100%	Not assessed	Not assessed	Not assessed	See above
Sollmann et al. (2018) [53]	17 – no controls	SRP permanent 5.9 %, transient 5.9 %	Not assessed	Not assessed	Not assessed	Not assessed	See above
This thesis	53/53 (1:1)	improved 52.8%; deteriorated 1.9%; SRP permanent 1.9%; transient 0% (n.s.)	GTR 90.6% (n.s.)	Not assessed	3.9±0.8 cm (n.s.)	DS 90±34 min; HS 8.6±3.9 days (n.s.)	See above

Table 8 c (continued) – Glioma

Reference	patients	Motor outcome	Resection	Survival	Craniotomy size	DS/HS	comments
Frey et al. (2014) [8]	250/115 (group-wise)	new deficits in 6.1/8.5% (n.s.)	GTR 58.6%/41.8%	PFS of LGG 15.5/12.4months, PFS of all glioma n.s.; OS n.s.	Not assessed	Not assessed	*PFS only significant for LGG – 18 vs. 38 patients*
Krieg et al. (2015) [21]	70/70 (paired- or group-wise unspecified)	improved: 4.3%/5.7%; deteriorated: 15.7%/31.4% (n.s.) SRP permanent 12.9%/25.7%; transient 8.6%/4.3% (n.s.)	GTR 65.7%/46.7%	OS for WHO°III and specific time points in WHO°IV	AP 5.2±1.1/ 6.1±1.9 cm Area 25.3±9.7/ 30.8±13.2 cm²	DS 201±57 min (n.s.) HS median 12/14 days	16/54 WHO°III/IV *Cave! adjuvant radiotherapy significantly different!!*
Picht et al. (2016) [39]	93/34	SRD transient 26%/3%; SRD permanent 13%; Improvement 9% (n.s.)	GTR 61%/45%	Not assessed	Not assessed	DS 228 min; HS pre-operative 3.2 days, post-operative 8.7 days (n.s.)	GBM WHO°IV; Prospective, controlled observational case-cohort study
Picht et al. (2013) [37]	11/11	9.1% deteriorated (n.s.)	GTR 10/11=90.9% nTMS vs. 0/3 controls	Change in tumor volume at 1 year* -(-67 to -100%)/(-56 to +40%)	Not assessed	Not assessed	Only WHO°II; only 3 controls had surgery
Rosenstock et al. (2017) [44]	113 – no controls	Improved 18.6% Deteriorated 15.0%	GTR 50%	Not assessed	Not assessed	Not assessed	17 LGG, 96 HGG
Sollmann et al., (2018) [53]	69 – no controls	SRP permanent 20.3 %, transient 4.3 %	Not assessed	Not assessed	Not assessed	Not assessed	20 LGG, 49 HGG
This thesis	53/53	improved 29.8%, deteriorated 12.8%; SRP permanent 12.8%; transient 4.3% (n.s.)	GTR 72.3%/53.2%	n.s. for nTMS, but significantly associated with GTR	4.8±1.2 cm (n.s.)	DS 126±56 min; HS 10.1±5.8 days (n.s.)	11 WHO°III, 36 WHO°IV

5.2. Strengths and limitations of this study

The present study analyses the largest collective of nTMS and control patients with different etiologies presented in the literature so far (127 nTMS and control patients each, including an additional test dataset of 127 bootstrap controls). It could be shown that a differentiation of entities – in particular, metastases and glioma – is eminently important, yielding different results particularly regarding gross total resection.

Still, a major limitation of this study remains its retrospective nature, which can possibly introduce bias due to changes in the surgical procedure, different surgeons, changing protocols for adjuvant therapy, etc.

As far as could be retrospectively determined, surgeons' experience, treatment according to the Stupp protocol [55], use of neuronavigation and intra-operative monitoring were largely uniform within the study period of 2009-2018. Moreover, there was some overlap between the nTMS and non-nTMS time eras, particularly during the implementation of nTMS in 2013. However, the 2016 WHO classification of central nervous system tumours has introduced molecular/genetic information, which was not available for all patients in the present analysis. These characteristics, such as IDH1-mutation status, may influence the survival analysis. Karnofksy performance scale was also not available for all patients and hence had to be excluded from the survival analysis. Instead, motor function was included, which provides at least one aspect of functional outcome.

To overcome the limitation inherent in the retrospective case-control design, chart review, radiological assessment, matching and analysis were revised by an attending neuroradiologist (PD Dr. Simgen) and an attending neurosurgeon (PD Dr. Hendrix). Great effort was invested to achieve ideal pair-matching. As a result, the matching quality of this study exceeds previous works. In Krieg et al. [20], the matching collective did not identically reproduce the preoperative motor status of the nTMS patients, with 34% of the nTMS patients presenting with preoperative paresis, but only 27% in the controls. Although this difference did not reach statistical significance ($p = 0.271$), it cannot be ruled out that some bias might have been introduced in the results. A similar difference was retained in the metastasis collectives in Krieg et al. [22], where 51.7% nTMS patients with preoperative paresis contrasted with 39.2% control patients (again, without statistical significance).

Frey et al. [8] and Krieg et al. [22] did not perform 1:1 matching, but rather compared two differently-sized cohorts, which were only matched group-wise. In their subsequent study [21], it is also unclear whether individual 1:1 matching or group-matching was performed. Although the lesion histology and preoperative motor status were rather well matched, the adjuvant therapy between the collectives was significantly different, so that conclusions about overall survival may have been biased.

In contrast to these studies, the present study performed rigorous 1:1 pair-matching of 127 nTMS cases to 127 best matches. Etiology and tumour location were identically matched, preoperative motor status was almost identical. To substantiate the observed outcome, a bootstrap analysis was performed. This could prove that the best match cohort is indeed representative of the complete historical collective of match candidates, and that the observed effects are not artifacts from sampling of the potential matches.

To date, there is only one controlled observational study on the clinical use of nTMS [39]. However, they present only a small collective of 34 control patients which is not 1:1 matched to the nTMS cases, and no survival data are available. The first randomized controlled trial of “nTMS for Motor Mapping of Rolandic Lesions (Motorstim)” is currently ongoing and recruiting patients with glioma and metastases (https://clinicaltrials.gov/ct2/NCT02879682).

5.3. Clinical relevance

This study has been able to contribute additional evidence to the clinical relevance of preoperative nTMS mapping in the resection of motor-eloquent brain lesions, specifically for malignant gliomas.

Increased overall gross total resection rates have been achieved in patients with malignant gliomas, with no detrimental effects on postoperative motor function. Although the present data set could not prove a significant association of nTMS with overall survival, GTR could be established as a significant prognostic variable for the collective of high-grade glioma patients, which provides an indirect link to nTMS insofar as GTR is again significantly associated with nTMS mapping.

Rosenstock et al. [44] and Sollmann et al. [53] have shown that a correlation exists between the proximity of motor-eloquent brain lesions to the cortico-spinal tract and the postoperative occurrence of surgery-related paresis in patients with high grade glioma (a similar result was obtained for fMRI by Krishnan et al. [24]). The interhemispheric ratio of the resting motor threshold was also found to be a marker of pathological excitability and hence increased functional hazard of the surgical procedure. Therefore, nTMS mapping may additionally provide valuable preoperative information on the risk of developing a paresis, which can be included in the decision-making process. This would be particularly useful if a similar risk assessment were found to apply to other entities, such as low-grade glioma. Here, a strategy of watchful waiting incurs the risks of developing functional deficits due to tumour growth, which must be balanced against the risk of surgery-related deficits and complications.

In the study on patients with low-grade glioma WHO°II presented by Picht et al. [37], the availability of nTMS maps changed surgical decision from watchful waiting to resection in 2/11 cases (18%) and towards more extensive resection in 4/11 cases (36%). Complete resection was achieved in 10/11 patients (91%). Wijnenga et al. [61] presented survival data on 228 patients with low-grade glioma, showing postoperative tumour volume as an independent prognostic factor in overall survival. A similar conclusion was drawn for glioblastoma multiforme by Stummer et al. [54]. Based on the available evidence, nTMS hence appears to offer the chance to achieve more complete resection without jeopardizing motor function.

In the collective of patients with metastases, no benefit for surgical or functional outcomes was observed. In contrast to glioma, cerebral metastases are often well demarcated from the surrounding healthy parenchyma and can hence be more easily be resected gross total without compromising neurological performance. Therefore, gross total resection rates may not be significantly improved by nTMS-mapping in the present metastasis collective. However, extent of infiltration and perifocal edema can vary with the primary tumour, so that both preoperative nTMS and intra-operative direct cortical stimulation can provide valuable information, and nTMS motor mapping can be useful for preoperative planning and the choice of surgical corridors [41;36].

For the relatively small subgroup of meningioma patients, no differences in terms of surgical outcomes were observed. In a recent study [43], it was argued that the presence of an arachnoidal cleavage plane could be predicted by a lower preoperative

resting motor threshold. Absence of edema, presence of an arachnoidal cleavage and the RMT were independent predictors of postoperative motor function. Based on these findings, nTMS may provide valuable additional information for meningioma surgery beyond a direct impact on extent of resection or motor outcome. In the present study, meningioma patients were mapped primarily if the meningioma appeared to infiltrate the primary motor cortex and/or the cerebrospinal tract, or in cases in which surgical resection was expected to require manoeuvering in direct vicinity of these structures. The nTMS information may hence have contributed to planning of the surgical strategy. It was estimated [43] that nTMS-based planning was considered useful in this context in 89.3% of cases, and led to a change in strategy in 42.5%. Whether additional improvements in surgical or functional outcome can be achieved in nTMS-based meningioma surgery requires further investigation.

5.4. Outlook: Subsequent studies

5.4.1. Application of nTMS information for radiotherapy planning

Preservation of neurological and cognitive abilities does not end with surgery. Modern radiotherapy allows for highly conformal dose shaping around the target volume while protecting surrounding radiosensitive structures (organs at risk, OAR's). Traditionally, cranial radiotherapy has placed great emphasis on reducing dose to the brainstem and medulla oblongata, optic nerves and chiasm, eyes and cochleae. Only recently have functional areas of the brain received increasing attention, first and foremost the hippocampus as an area of ongoing neurogenesis in the adult brain. Radiation dose to the hippocampus or to the whole brain including the hippocampi has been associated with neurocognitive impairment [10-11;18;29;32;59]. The motor cortex as a possible site of radiation-induced functional impairment has been less frequently studied. Park et al. [33] reported motor deficits after high-dose Gamma-Knife stereotactic radiosurgery to sites close to the motor cortex. Pfeiffer et al. [34] postulated a relationship between higher dose to the precentral gyrus with functional deficits in executive function, attention and verbal and working memory.

A small number of studies with limited patient collectives have included nTMS information on the motor cortex for radiotherapy planning [5;17;38;51;58]. However, none of them included both the nTMS-based motor cortex and the hippocampi in the

optimization. A systematic evaluation of different planning techniques both for the treatment of brain metastases and malignant glioma is still lacking.

As an application of the nTMS data from the Department of Neurosurgery, we are therefore currently implementing the nTMS-based motor cortex as a potentially radiation-sensitive volume into radiotherapy treatment planning. A first evaluation was performed for the patients with brain metastases presented in this thesis, 24 of whom received stereotactic radiation therapy at the Department of Radiotherapy. For each patient, two re-optimized plans were created: a “motor” plan sparing the nTMS-based motor cortex, and a “motor & hipp” plan additionally reducing the dose to the hippocampus. Figure 11 shows two examples for dose distributions compared with the original radiotherapy plan.

It could be shown that – from a radiotherapeutic perspective – clinically acceptable treatment plans can be created with significantly improved dosimetric protection of the motor cortex and ipsilateral hippocampus.

In re-optimized plan scenarios (only nTMS and nTMS plus hippocampus), the mean dose to the nTMS-derived motor cortex could be reduced by approximately 3 Gy (30%, $p < 0.001$) as compared with the original clinically accepted plan (Fig. 12). When the hippocampus was included in the optimization, the mean and maximum dose to the ipsilateral hippocampus could be reduced by ca. 0.3 Gy and 0.7 Gy, respectively ($p = 0.003$ and 0.007). This amounts to ca. 23% and 27% of the already rather low hippocampus dose for cortically located lesions. Other organs at risk and the coverage of the planning target volume remained unimpaired in both re-optimized planning scenarios.

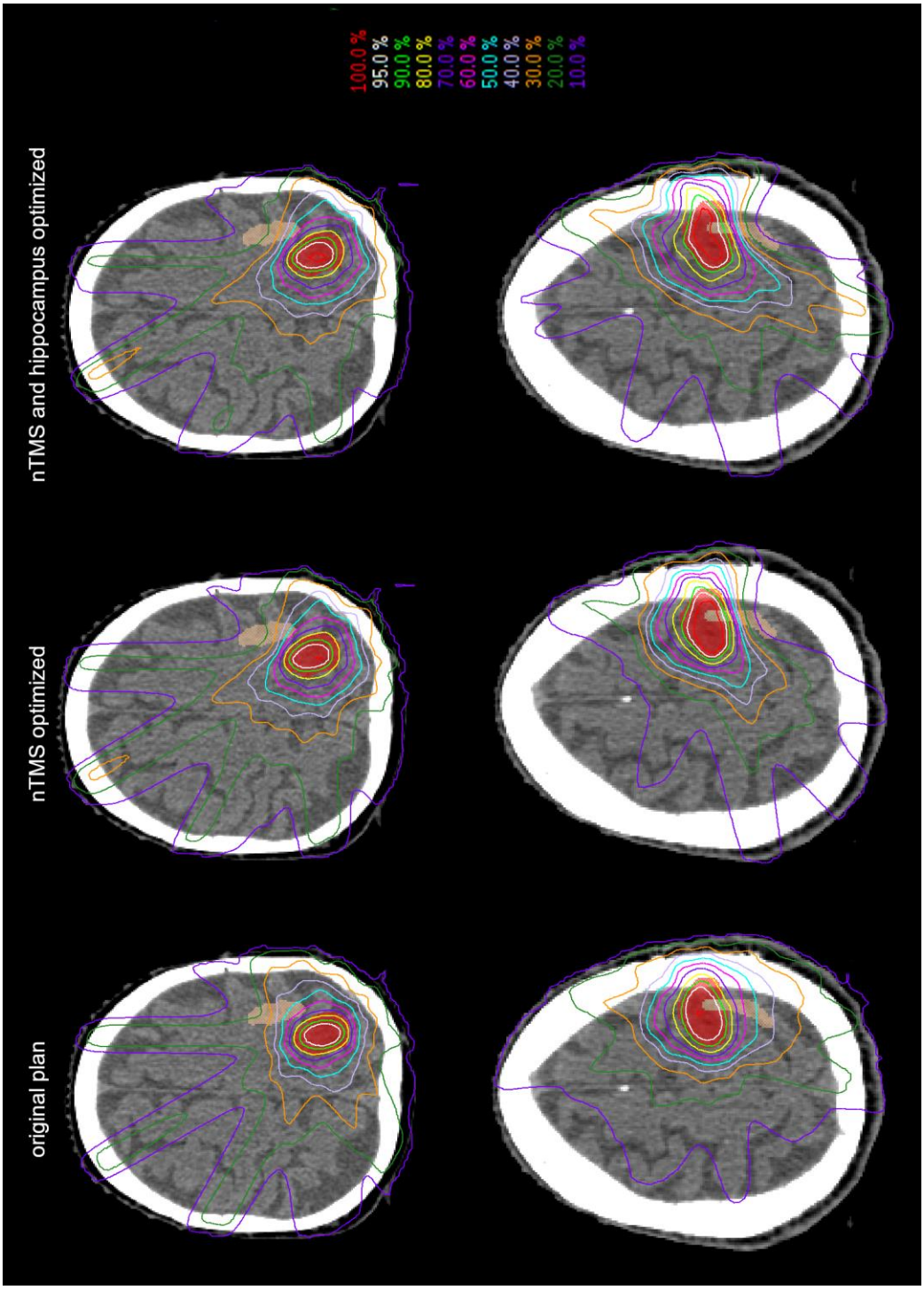


Figure 11. Example dose distributions (axial slices), together with the planning target volume (PTV) in red colourwash and the nTMS-based motor cortex avoidance volume (MCAV) in skin colour. For the upper patient, there was a minimum distance of 4 mm between PTV and MCAV, for the patient in the lower panel, the two volumes overlapped partly (92.5 % of the MCAV was located outside the PTV). Isodose lines are given relative to the prescription dose in the isocenter.

Importantly, in the plans with only motor cortex sparing, a higher dose resulted for the ipsilateral hippocampus than in the original plans (Figure 12). This may be more detrimental to overall functional status and quality of life than the advantage gained by sparing the motor cortex alone, particularly since the neural stem cells in the dentate gyrus may react to considerably lower radiation doses than the post-mitotic neurons in the motor cortex. Most crucially, there is no inherent trade-off in the optimization of these two structures, so protection of the motor cortex as well as the hippocampi is feasible at no detriment in dosimetric plan quality, provided that both structures are included in the planning process.

Ongoing studies are currently exploring the potential of motor cortex and hippocampus preservation in the irradiation of primary brain tumours, particularly malignant glioma, and to explore the possibility of including also additional nTMS information on language-eloquent brain regions and information from tractography.

Within this ongoing work programme, it also remains to be established whether the dosimetric improvements translate into a clinical benefit for the patients in terms of quality of life, cognitive or motor performance.

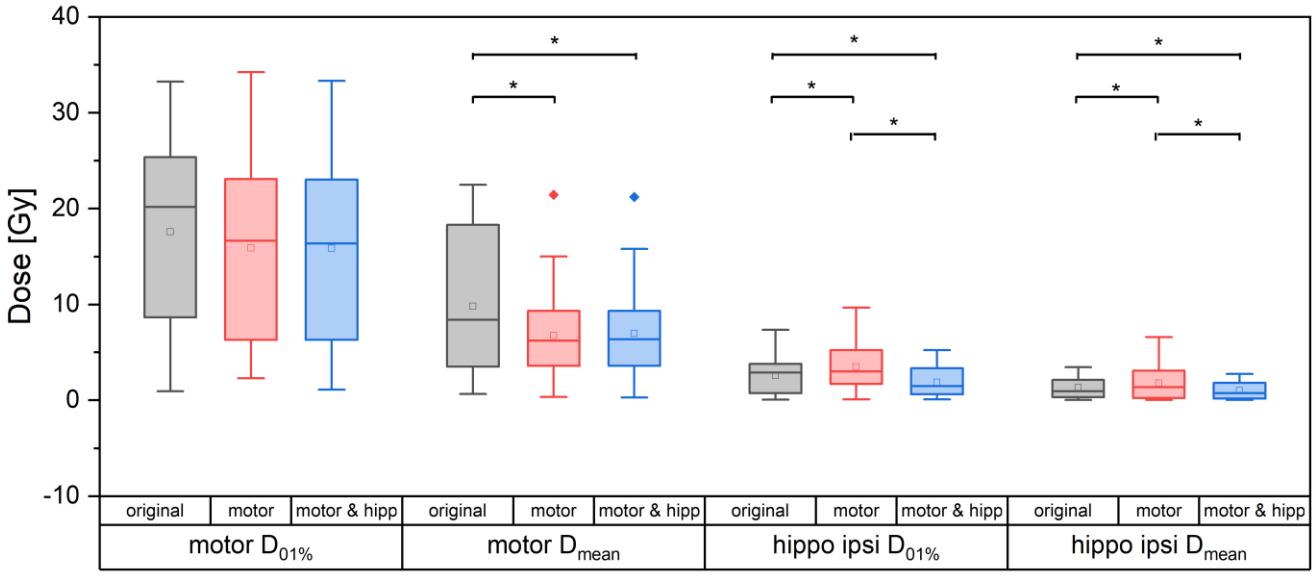


Figure 12. Dose to motor cortex and hippocampus in the three scenarios. Both the average dose and maximum dose (assessed by D1%, i.e. the dose received by 1% of the organ volume) are evaluated for the original plans and the reoptimized scenarios.

5.4.2. Influence of motor cortex protection on cognitive function and quality of life

There is no doubt that a better postoperative motor function greatly influences the patients' quality of life, independence and participation in social and working life. Beyond this, better postoperative performance may also allow for an earlier start of adjuvant treatment, which may again be associated with increased survival in addition to the effect of improved gross total resection. Furthermore, the past years have raised awareness that physical activity – which will be promoted by better motor performance – presents an important factor for well-being, reduction of fatigue and depression and increased overall survival of cancer patients [2;9]. Beyond these consequences, there are increasing indications that exercise and motor function may be directly associated with improved cognitive performance [3-4;14;62].

Based on this hypothesis, it would be desirable to assess cognitive function together with motor function after surgery and over the course of adjuvant therapy and follow-up. Clinical studies are required to establish a link between the surgical and dosimetric protection of functional cortical areas and clinical outcome regarding motor and cognitive function and help preserve patient's health-related quality of life.

6. Conclusions

The implementation of preoperative nTMS maps facilitates increased rates of gross total resection without compromising motor function in patients suffering from malignant gliomas. For the subgroups of metastases, meningiomas and cavernomas no differences regarding motor outcome or resection rates were observed.

18-months survival in patients with malignant glioma was significantly associated with age < 60 years and achievement of gross total resection. Among malignant glioma, gross total resection itself was independently predicted by availability of preoperative nTMS motor maps, smaller lesion size and better preoperative motor performance.

Since gross total resection is a critical factor for survival in malignant glioma, implementing nTMS-mapping might translate into a beneficial overall survival due to improved surgical results.

7. List of Abbreviations

BMRC	British Medical Research Council
BS	bootstrap
CI	confidence interval
CNS	central nervous system
CT	computed tomography
DCS	direct cortical stimulation
DH	duration of hospital stay
DS	duration of surgery
DWI	diffusion-weighted imaging
EMG	electromyography
FDG	fluor-desoxyglucose
FLAIR	fluid-attenuated inversion recovery
fMRI	functional magnetic resonance imaging
GBM	glioblastoma multiforme
GTR	gross total resection
HGG	high-grade glioma
HS	hospital stay
IDH	isocitrate dehydrogenase
IR	infrared
LGG	low-grade glioma
MCAV	motor-cortex avoidance volume
MEG	magnetoencephalography
MEP	motor-evoked potential
MGMT	O6-methylguanin-DNA-methyl transferase
MPRage	magnetization-prepared rapid gradient echo
MRI	magnetic resonance imaging
n/c	not calculated
n.s.	not significant
NBS	navigated brain stimulation
nTMS	navigated TMS
OAR	organ at risk
OR	odds ratio
OS	overall survival
PACS	picture archiving and communication system
PET	positron emission tomography
POD	post-operative day

PFS	progression-free survival
PTV	planning target volume
RMT	resting motor threshold
ROI	region of interest
SPECT	single-photon emission computed tomography
SRD	surgery-related deficit
SRP	surgery-related paresis
TMS	transcranial magnetic stimulation
TTF	Tumour-Treating Fields
WHO	World Health Organization

8. References

1. Barker AT, Janlinous R, Freeston IL (1985) Non-invasive magnetic stimulation of human motor cortex. Lancet 1:1106-1107

2. Cormie P, Nowak AK, Chambers SK, Galvão DA, Newton RU (2015) The potential role of exercise in neuro-oncology. Front Oncol 5(85)

3. Cotman CW, Berchtold NC (2002) Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends Neurosci* 25:295-301

4. Cotman CW, Berchtold NC, Christie L-A (2007) Exercise builds brain health: key roles of growth factor cascades and inflammation. *Trends Neurosci* 30:464-472

5. Diehl CD, Schwendner MJ, Sollmann N, Oechsner M, Meyer B, Combs SE, Krieg SM (2019) Application of presurgical navigated transcranial magnetic stimulation motor mapping for adjuvant radiotherapy planning in patients with high-grade gliomas, *Radiother Oncol* 138:30-37

6. Duffau H, Lopes M, Arthuis F, et al. (2005) Contribution of intraoperative electrical stimulation in surgery of low grade gliomas: a comparative study between two series without (1985-96) and with (1996-2003) functional mapping in the same institution. *J Neurol Neurosurg Psychiatry* 76(6):845-851

7. Efron B, Tibshirani R (1986) Bootstrap methods for standard errors, confidence intervals, and other measures of statistical accuracy. *Stat Sci* 1:54-77

8. Frey D, Schilt S, Strack V, Zdunczyk A, Rösler J, Niraula B, Vajkoczy P, Picht T (2014) Navigated transcranial magnetic stimulation improves the treatment outcome in patients with brain tumors in motor eloquent locations. *Neuro-Oncology* 16(10):1365-1372

9. Gehring K, Stuiver MM, Visser E, Kloek C, van den Bent M, Hanse M, Tijssen C, Rutten G-J, Taphoorn MJB, Aaronson NK, Sitskoorn MM (2020) A pilot randomized controlled trial of exercise to improve cognitive performance in patients with stable glioma: a proof of concept, *Neuro-Oncol* 22(1):103-115

10. Gondi V, Hermann BP, Mehta MP, Tomé WA (2013) Hippocampal Dosimetry Predicts Neurocognitive Function Impairment After Fractionated Stereotactic Radiotherapy for Benign or Low-Grade Adult Brain Tumors, *Int J Radiat Oncol Biol Phys* 85(2):348-354

11. Gondi V, Pugh SL, Tome WA, Caine C, Corn B, Kanner A, Rowley VK, DeNittis A, Greenspoon JN, Konski AA, Baumann GS, Shah S, Shi W, Wendland M, Kachnik L, Mehta MP (2014) Preservation of Memory With Conformal Avoidance of the Hippocampal neural Stem-Cell Compartment During Whole-Brain Radiotherapy for Brain Metastases (RTOG 0933): A Phase II Multi-Institutional Trial, *J Clin Onc* 32(34):3810-3816

12. Hendrix P, Senger S, Griessenauer CJ, Simgen A, Schwerdtfeger K, Oertel J (2016) Preoperative Navigated Transcranial Magnetic Stimulation in Patients with Motor Eloquent Lesions with Emphasis on Metastasis. *Clin Anat* 29:925-931

13. Hendrix P, Senger S, Griessenauer CJ, Simgen A, Linsler S, Oertel J (2017) Preoperative navigated transcranial magnetic stimulation and tractography in transparietal approach to the trigone of the lateral ventricle, *J Clin Neurosci* 41:154-161

14. Herold F, Törpel A, Schega L, Müller NG (2019) Functional and/or structural brain changes in response to resistance exercises and resistance training leads to cognitive improvements – a systematic review. *Eur Rev Aging Phys* Act 16:10

15. Hou BL, Bradbury M, Peck KK; Petrovich NM, Gutin PH, Holodny AI (2006) Effect of brain tumor neovasculature defined by rCBV on BOLD fMRI activation volume in the primary motor cortex. *Neuroimage* 32:489-497

16. Ilmoniemi RJ, Ruohonen J, Karhu J (1999) Transcranial Magnetic Stimulation – A New Tool for Functional Imaging of the Brain. *Crit Rev Biomed* Eng. 27(3-5):241-284

17. Islam M, Cooray G, Benmakhlouf H, Hatiboglu M, Sinclair G (2020) 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, *Surg Neurol Int* 11(29):1-11

18. Kim KS, Wee CW, Seok J-Q, Hong JW, Chung J-B, Eom K-Y, Kim J-S, Kim C-Y, Park YH, Kim YJ, Kim IA (2018) Hippocampus-sparing radiotherapy using volumetric modulated arc therapy (VMAT) to the primary brain tumor: the result of dosimetric study and neurocognitive function assessment. *Radiat Oncol* 13:29

19. Komori T (2017) The 2016 WHO Classification of Tumours of the Central Nervous System: The Major Points of Revision. *Neurol Med Chir (Tokyo)* 57:301-311.

20. Krieg SM, Sabih J, Bulubasova L, Obermueller T, Negwer C, Janssen I, Shiban E, Meyer B, Ringel F (2014) Preoperative motor mapping by navigated transcranial magnetic brain stimulation improves outcome for motor eloquent lesions. *Neuro-Oncol* 16(9):1274-1282

21. Krieg SM, Sollmann N, Obermueller T, Sabih J, Bulubas L, Negwer C, Moser T, Droese D, Boeckh-Behrens T, Ringel F, Meyer B (2015) Changing the clinical course of glioma patients by preoperative motor mapping with navigated transcranial magnetic brain stimulation. *BMC Cancer* 15:231

22. Krieg SM, Picht T, Sollmann N, Bährend I, Ringel F, Nagarajan SS, Meyer B, Tarapore PE (2016) Resection of Motor Eloquent Metastases Aided by Preoperative nTMS-Based Motor Maps – Comparison of Two Observational Cohorts. *Front Oncol* 6:261.

23. Krieg SM, Lioumis P, Mäkelä JP, Wilenius J, Karhu J, Hannula H, Savolainen P, Weiss Lucas C, Seidel K, Laakso A, Islam M, Vaalto S, Lehtinen H, Vitikainen A-M, Tarapore PE, Picht T (2017) Protocol for motor and language mapping by navigated TMS in patients and healthy volunteers; workshop report. *Acta Neurochir* 159:1187-1195

24. Krishnan R, Raabe A, Hattingen E, Szelényi A, Yahya H, Hermmann E, Zimmermann M, Seifert V (2004) Functional magnetic resonance imaging-integrated neuronavigation: Correlation between lesion-to-motor cortex distance and outcome. *Neurosurgery* 55:904-915

25. Lefaucheur JP (2010) Why image-guided navigation becomes essential in the practice of transcranial magnetic stimulation. *Neurophysiol clin* 40:1-5

26. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P (2007) The 2007 WHO Classification of Tumours of the Central Nervous System. *Acta Neuropathol* 114:97-109.

27. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW (2016) The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol* 131:803-820.

28. Lu-Emerson C, Eichler AF (2012) Brain metastases. *Continuum* (Minneap Minn) 18(2):295-311.

29. Ma TM, Grimm J, McIntyre R, Anderson-Keightly H, Kleinberg LR, Hales RK, Moore J, Vannorsdall T, Redmond KJ (2017) A prospective evaluation of hippocampal radiation dose volume effects and memory deficits following cranial irradiation, R*adiother Oncol* 125:234-240

30. Mühl-Benninghaus R (2017) Extraaxiale Tumoren des zentralen Nervensystems. *Radiologe* 57:715-727.

31. Papanagiotou P, Ketter R, Reith W (2012) Extraaxiale Hirntumoren. *Radiologe* 52:1129-1146.

32. Parihar VK, Limoli CL (2013) Cranial irradiation compromises neuronal architecture in the hippocampus, *PNAS* 110(31):12822-12827

33. Park C-Z, Choi H-Y, Lee S-R, Roh T H, Seo M-R, Kim S-H (2016) Neurological Change after Gamma Knife Radiosurgery for Brain Metastases Involving the Motor Cortex, *Brain Tum Res Treat* 4(2):111-115

34. Pfeiffer AM, Leyrer CM, Greene-Schloesser DM, Shing E, Kearns WT, Hinson WH, Tatter SB, Ip EH, Rapp SR, Robbins ME, Shaw EG, Chang MD (2013) Neuroanatomical target theory as a predictive model for radiation-induced cognitive decline, *Neurology* 80:747-753

35. Picht T, Mularski S, Kuehn B, Vajkoczy P, Kombos T, Suess O (2009) Navigated Transcranial Magnetic Stimulation for Preoperative Functional Diagnostic in Brain Tumor Surgery. *Neurosurgery* 65(ONS Suppl 1):ons93-ons99

36. Picht T, Schmidt S, Brandt S et al (2011) Preoperative functional mapping for Rolandic brain tumor surgery: comparison of navigated transcranial magnetic stimulation to direct cortical stimulation. *Neurosurgery* 69:581-589

37. Picht T, Schulz J, Vajkoczy P (2013) The preoperative use of navigated transcranial magnetic stimulation facilitates early resection of suspected low-grade gliomas in the motor cortex. *Acta Neurochir* 155:1813-1821.

38. Picht T, Schilt S, Frey D, Vajkoczy P, Kufeld M (2014) Integration of navigated brain stimulation data into radiosurgical planning: potential benefits and dangers, *Acta Neurochir* 156:1125-1133

39. Picht T, Frey D, Thieme S, Kliesch S, Vajkocy P (2016) Presurgical navigated TMS motor cortex mapping improves outcome in glioblastoma surgery: a controlled observational study*. J Neurooncol* 126:535-543

40. Raffa G, Bährend I, Schneider H, Faust K, Germanò A, Vajkoczy P, Picht T (2016) A Novel Technique for Region and Linguistic Specific nTMS-based DTI Fiber Tracking of Language Pathways in Brain Tumor Patients. *Front Neurosci* 10:552

41. Raffa G, Conti A, Scibilia A, et al. (2018) The Impact of Diffusion Tensor Imaging Fiber Tracking of the Corticospinal Tract Based on Navigated Transcranial Magnetic Stimulation on Surgery of Motor-Eloquent Brain Lesions. Neurosurgery 83(4):768-782.

42. Raffa G, Scibilia A, Conti A, Ricciardo G, Rizzo V, Morelli A, Angileri FF, Cardali SM, Germanò A (2019) The role of navigated transcranial magnetic stimulation for surgery of motor-eloquent brain tumors: a systematic review and meta-analysis. *Clin Neurol Neurosurg* 180:7-17

43. Raffa G, Picht T, Scibilia A, Rösler J, Rein J, Conti A, Ricciardo G, Cardali SM, Vajkoczy P, Germanò A (2020) Surgical treatment of meningiomas located in the Rolandic area: the role of navigated transcranial magnetic stimulation for preoperative planning, surgical strategy, and prediction of arachnoidal cleavage and motor outcome. *J Neurosurg* 133:107-118

44. Rosenstock T, Grittner U, Acker G, Schwarzer V, Kulchytska N, Vajkoczy P, Picht T (2017) Risk stratification in motor area-related glioma surgery based on navigated transcranial magnetic stimulation data. *J Neurosurg* 126:1227-1237

45. Rossini PM, Barker AT, Berardelli A, Caramia MD, Caruso G, Cracco RQ, Dimitrijevic MR, Hallett M, Katayama Y, Lücking CH, Maertens de Noordhout AL, Marsden CD, Murray NMF, Rothwell JC, Swash M, Tomberg C (1994) Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroenceph Clin Neurophysiol* 91:79-92

46. Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, Di Lazzaro V, Ferreri F, Fitzgerald PB, George MS, Hallett M, Lefaucheur JP, Langguth B, Matsumoto H, Miniussi C, Nitsche MA, Pascual-Leone A, Paulus W, Rossi S, Rothwell JC, Siebner HR, Ugawa Y, Walsh V, Ziemann U (2015) Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. *Clin Neurophysiol* 126:1071-1107

47. Rothwell J (2018) Transcranial brain stimulation: Past and future. *Brain Neurosci Adv* 2:1-4

48. Ruohonen (1998) Transcranial Magnetic Stimulation: Modelling and New Techniques. Dissertation, Helsinki University of Technology, Espoo, Finland

49. Ruohonen J, Karhu J (2010) Navigated transcranial magnetic stimulation. *Neurophysiol clin* 40:7-17

50. Rutten GJ, Ramsey NF (2010) The role of functional magnetic resonance imaging in brain surgery. *Neurosurg Focus* 28(2):E4

51. Schwendner MJ, Sollmann N, Diehl CD, Oechsner M, Meyer B, Krieg SM, Combs SE (2018) The Role of Navigated Transcranial Magnetic Stimulation Motor Mapping in Adjuvant Radiotherapy Planning in Patients With Supratentorial Brain Metastases, *Front Oncol* 8:424

52. Sollmann N, Meyer B, Krieg SM (2017) Implementing Functional Preoperative Mapping in the Clinical Routine of a Neurosurgical Department: Technical Note. *World Neurosurg* 103:94-105

53. Sollmann N, Wildschuetz N, Kelm A, Conway N, Moser T, Bulubas L, Kirschke JS, Meyer B, Krieg SM (2018) Associations between clinical outcome and navigated transcranial magnetic stimulation characteristics in patients with motor-eloquent brain lesions: a combined navigated transcranial magnetic stimulation–diffusion tensor imaging fiber tracking approach. *J Neurosurg* 128:800-810

54. Stummer W, Reulen H-J, Meinel T, Pichlmeier W, Schumacher W, Tonn J-C, Rohde V, Oppel F, Turowski B, Woiciechowsky C, Franz K, Pietsch T, ALA-Glioma Study Group (2008) Extent of Resection and Survival in Glioblastoma Multiforme: Identification of and Adjustment for Bias. *Neurosurg* 62(3):564-576

55. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJB, Janzer RC, Ludwin SK, Allgeier A, Fisher B, Belanger K et al (2009) Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival of glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol* 10:459-466

56. Takahashi S, Wajkoczy P, Picht T (2013) Navigated transcranial magnetic stimulation for mapping the motor cortex in patients with rolandic brain tumors. *Neurosurg Focus* 34(4):E3

57. Tarapore PE, Tate MC, Findlay AM, Honma SM, Mizuiri D, Berger MS, Nagarajan SS (2012) Preoperative multimodal motor mapping: a comparison of magnetoencephalography imaging, navigated transcranial magnetic stimulation, and direct cortical stimulation. *J Neurosurg* 117:354-362.

58. Tokarev AS, Rak VA, Sinkin MV, Evdokimova EL, Stepanov VN, Koynash GV, Krieg SM, Krylov VV (2020) Appliance of Navigated Transcranial Magnetic Stimulation in Radiosurgery of Brain Metastases, *J Clin Neurophysiol* 37(1):50-55

59. Tsai P-F, Yang C-C, Chuang C-C, Huang T-Y, Wu Y-M, Pai P-C, Tseng C-K, Wu T-H, Shen Y-L, Lin S-Y (2015) Hippocampal dosimetry correlates with the change in neurocognitive function after hippocampal sparing during whole brain radiotherapy: a prospective study. *Radiat Oncol* 10:253

60. Wesseling P, Capper D (2017) WHO 2016 Classification of gliomas. *Neuropathol Appl Neurobiol* 44(2):139-150.

61. Wijnenga MMJ, French PJ, Dubbink HJ, Dijnens WNM, Atmodimedjo PN, Kros JM, Smits M, Gahrmann R, Rutten G-J, Verheul JB, Fleischeuer R, Dirven CMF, Vincent ANPE, van den Bent MJ (2018) The impact of surgery in molecularly defined low-grade glioma: an integrated clinical, radiological, and molecular analysis, *Neuro-Oncol* 20(1):103-112.

62. Wilke J, Giesche F, Klier K, Vogt L, Herrmann E, Banzer W (2019) Acute Effects of Resistance Exercise on Cognitive Function in Healthy Adults: A Systematic Review with Multilevel Meta-Analysis. *Sports Med Auckl NZ* 49:905-916

63. Zweckberger K, Unterberg AW (2012) Neurochirurgie. In: Siewert JR, Stein HJ (eds) Chirurgie. 9. Auflage, Springer, Berlin Heidelberg, pp.187-273.

64. Zyck S, Gould GC (2020) Cavernous Venous Malformation. In StatPearls (Internet). Treasure Island (FL): StatPearls Publishing, 2020 Jan.

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11. Appendix

A.1 Further surgical and functional endpoints of the nTMS collective

An overview of tumour and edema volumes, craniotomy area and in-hospital stay after surgery is given in Figure A1 for the nTMS patients.

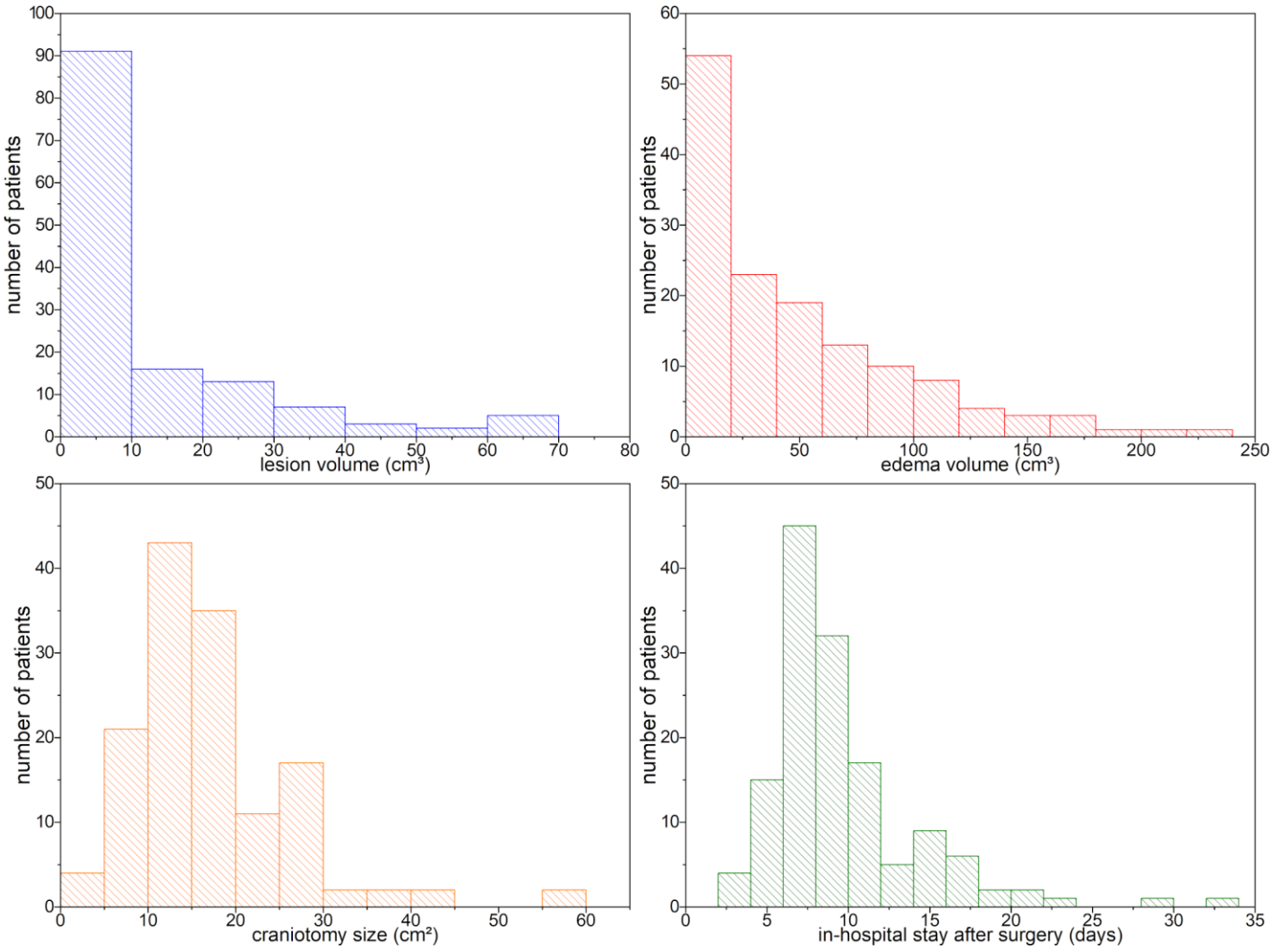


Figure A 1. Tumour and edema volume, craniotomy area and hospital stay for nTMS group.

The distribution of BMRC rank in the nTMS group prior to surgery, at discharge from hospital (approximately on day 7) and during follow-up (6 weeks to 3 months postoperatively) is shown in Figure A2.

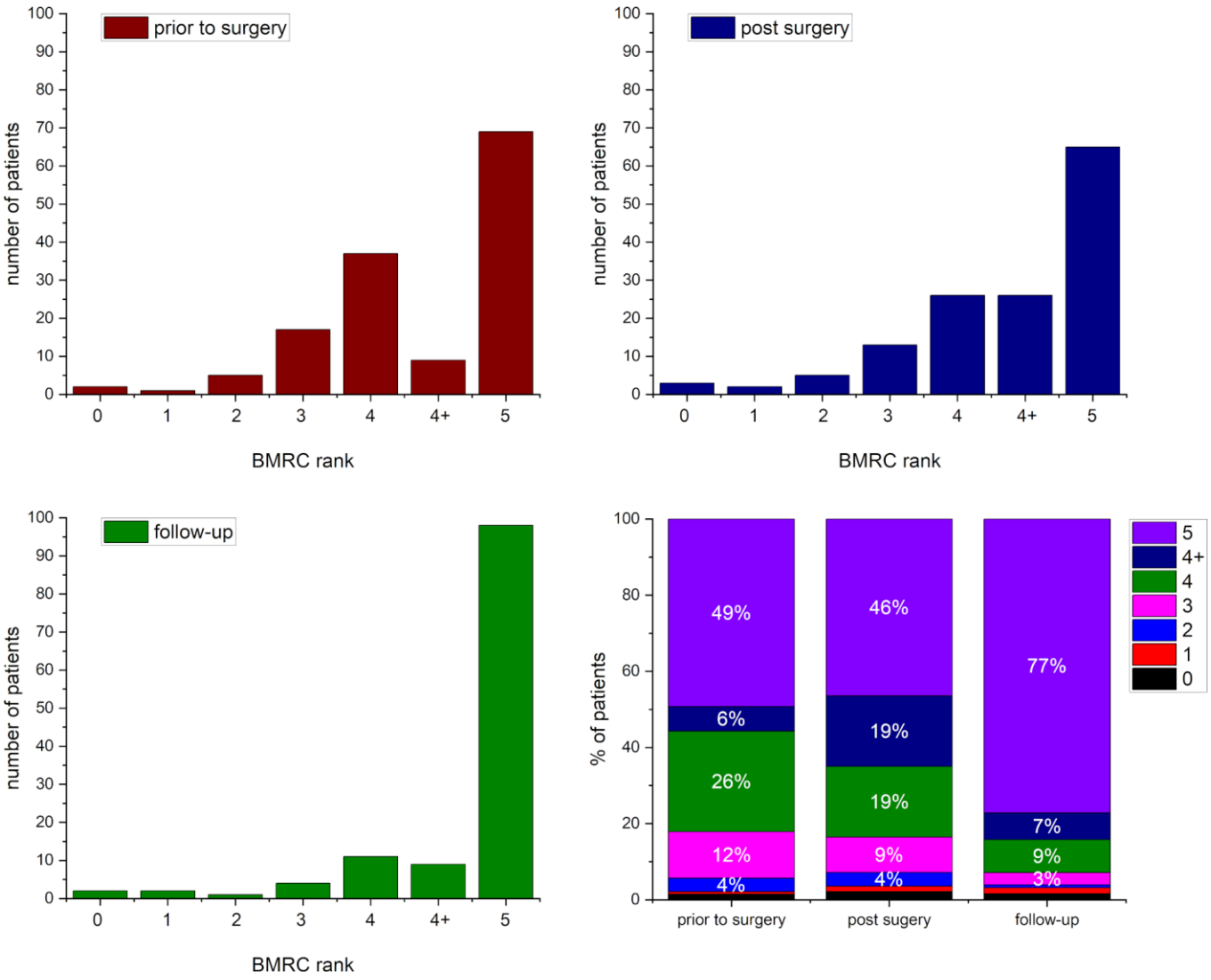


Figure A 2. Distribution of BMRC ranks pre-operatively, at discharge (day 7) and follow-up (day 60). The difference between pre- and postoperative motor function did not reach statistical significance, but there was a significant improvement at follow-up day 60.

It was tested whether the change in BMRC rank from baseline to follow-up correlated with the size of the tumour or edema, craniotomy area or hospital stay after surgery

using Pearson's coefficient of correlation. However, no significant association between these variables could be found.

When comparing the different tumour entities, no significant difference in preoperative motor status was observed between metastases and malignant glioma; meningioma presented with significantly better preoperative motor function (75 % patients without motor impairment at presentation, p = 0.019 when comparing meningioma with GBM, p = 0.016 when comparing meningioma with metastasis). In follow-up, no significant difference was retained, which may be caused by the improvement in motor performance of the metastases and malignant glioma groups, which was significant when compared to baseline for glioma (p = 0.02) and metastases (p < 0.001), but not for meningioma (Figure A3). Although some improvement was also observed for the meningioma patients, this failed to reach statistical significance, possibly due to the small number of patients.

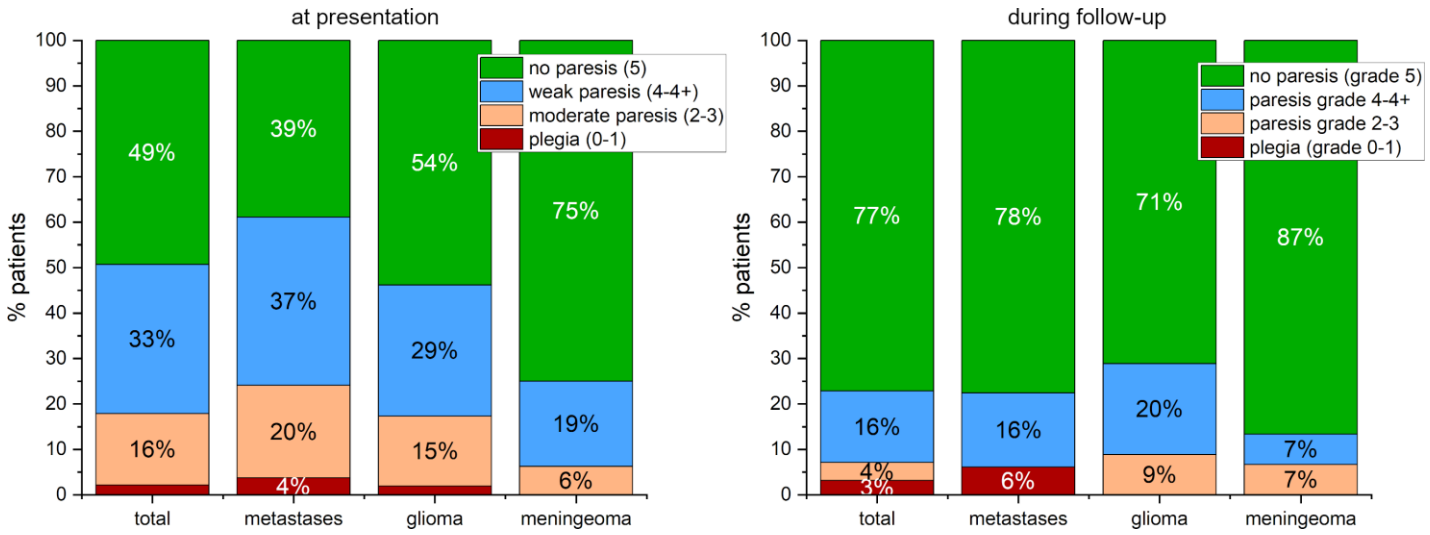


Figure A 3. Motor status at baseline and during follow-up (day 60) by entity. For easier comparison, pareses were grouped into categories.

A.2 Subgroup analyses

To avoid bias by the inclusion of small groups of entities such as cavernoma or meningioma, the analysis was repeated for reduced data collectives:

1. complete dataset of **intra-axial brain lesions** (111 patients), i.e. excluding meningioma patients

Table A 1. Intra-axial brain lesions: 111 patients with glioma, metastasis, or cavernoma

	nTMS group (n=111)	best match (n=111)	p-value
Age [y] (M ± SD)	61.4 ± 14.8	59.7 ± 13.7	0.316
Sex			
Female	49 (44.1%)	37 (33.3 %)	0.096
Male	62 (55.9%)	74 (66.7 %)	
Preoperative motor function			
No paresis	51 (45.9%)	53 (47.8%)	0.435
Mild paresis	38 (34.2%)	38 (34.2%)	
Severe paresis	22 (19.8%)	20 (18.0%)	
BMRC (M ± SD)	4.2 ± 1.0	4.2 ± 1.0	0.899
Location			
Frontal	78 (70.3%)	77 (69.4%)	0.884
Parietal	33 (29.7%)	34 (30.6%)	
Lesion size			
Diameter [Ø in cm]	2.5 ± 1.1	2.6 ± 1.2	0.159
Volume [cm³]	12.7 ± 14.9	14.9 ± 17.3	0.121
Postoperative motor function			
POD 7 BMRC (M ± SD)	4.2 ± 1.0	4.3 ± 1.1	0.534
POD 60 BMRC (M ± SD)	4.6 ± 1.0	4.6 ± 1.0	0.722
Improved	49 (38.6% of 127 76.6% of 64)	50 (39.4 % of 127 78.1% of 64)	0.833
Unchanged	68 (53.5%)	66 (52.0%)	0.802
Deteriorated	10 (7.9%)	11 (8.7%)	0.820
Surgery-related paresis			
None	112 (88.2%)	111 (87.4%)	0.848
Transient paresis	5 (3.9%)	5 (3.9%)	1.000
Permanent paresis	10 (7.9%)	11 (8.7%)	0.820
Gross total resection	107 (84.3%)	93 (73.2%)	**0.030**
Craniotomy size [Ø diameter in cm ± SD]	4.4 ± 1.1	4.6 ± 1.2	0.071
Duration of surgery [Ø in mins ± SD]	115 ± 56	126 ± 58	0.124
Hospital stay [Ø in days ± SD]	9.0 ± 4.7	8.9 ± 5.8	0.878

2. dataset of only **intra-axial brain tumours** (105 patients), i.e. excluding meningioma and cavernoma

Table A 2. Intra-axial brain tumours: 105 patients with glioma or metastasis

	nTMS group (n=105)	best match (n=105)	p-value
Age [y] (M ± SD)	62.5 ± 14.1	60.9 ± 12.6	0.369
Sex			
Female	46 (43.8%)	36 (34.3%)	0.155
Male	59 (56.2%)	69 (65.7%)	
Preoperative motor function			
No paresis	47 (44.8%)	48 (45.7%)	0.515
Mild paresis	37 (35.2%)	38 (36.2%)	
Severe paresis	21 (20.0%)	19 (18.1%)	
BMRC (M ± SD)	4.2 ± 1.0	4.2 ± 1.0	1
Location			
Frontal	75 (71.4%)	75 (71.4%)	1
Parietal	30 (28.6%)	30 (28.6%)	
Lesion size			
Diameter [Ø in cm]	2.6 ± 1.1	2.7 ± 1.2	0.264
Volume [cm^3]	13.3 ± 15.1	15.3 ± 17.6	0.168
Postoperative motor function			
POD 7 BMRC (M ± SD)	4.2 ± 1.0	4.2 ± 1.2	0.892
POD 60 BMRC (M ± SD)	4.5 ± 1.1	4.5 ± 1.1	0.611
Improved	43 (41.0% of 105 74.1% of 58)	43 (41.0 % of 105 75.4% of 57)	0.872
Unchanged	54 (51.4%)	53 (50.5%)	0.890
Deteriorated	8 (7.6%)	9 (8.6%)	0.800
Surgery-related paresis			
None	95 (90.5%)	93 (88.6%)	0.652
Transient paresis	2 (1.9%)	3 (2.9%)	0.651
Permanent paresis	8 (7.6%)	9 (8.6%)	0.800
Gross total resection	86 (81.9%)	73 (69.5%)	**0.035**
Craniotomy size [Ø diameter in cm ± SD]	4.3 ± 1.1	4.5 ± 1.1	0.078
Duration of surgery [Ø in mins ± SD]	111 ± 55	120 ± 53	0.233
Hospital stay [Ø in days ± SD]	9.2 ± 4.9	9.1 ± 6.3	0.903

3. dataset of only **intra-axial malignant tumours** (100 patients), i.e. excluding meningioma, cavernoma and low-grade glioma

Table A 3. Intra-axial malignant tumours: 100 patients with malignant glioma (WHO°III/IV) or metastasis

	nTMS group (n=100)	best match (n=100)	p-value
Age [y] (M ± SD)	63.4 ± 13.7	61.4 ± 11.9	0.278
Sex			
Female	43 (43%)	34 (34%)	0.189
Male	57 (57%)	66 (66%)	
Preoperative motor function			
No paresis	43 (44.0%)	44 (44.0%)	0.657
Mild paresis	37 (37.0%)	37 (37.0%)	
Severe paresis	20 (20.0%)	19 (19.0%)	
BMRC (M ± SD)	4.1 ± 1.0	4.1 ± 1.0	0.894
Location			
Frontal	71 (71.0%)	71 (71.0%)	1
Parietal	29 (29.0%)	29 (29.0%)	
Lesion size			
Diameter [Ø in cm]	2.5 ± 1.1	2.6 ± 1.2	0.459
Volume [cm^3]	13.2 ± 15.4	14.9 ± 17.7	0.252
Postoperative motor function			
POD 7 BMRC (M ± SD)	4.2 ± 1.0	4.2 ± 1.2	0.945
POD 60 BMRC (M ± SD)	4.5 ± 1.1	4.4 ± 1.2	0.560
Improved	42 (42.0% of 100 73.7% of 57)	42 (42.0% of 100 75.0% of 56)	0.873
Unchanged	51 (51.0%)	49 (49.0%)	0.777
Deteriorated	7 (7.0%)	9 (9.0%)	0.602
Surgery-related paresis			
None	91 (91.02%)	88 (88.0%)	0.488
Transient paresis	2 (2.0%)	3 (3.0%)	0.650
Permanent paresis	7 (7.0%)	9 (9.0%)	0.602
Gross total resection	82 (82.0%)	71 (71.0%)	0.064
Craniotomy size [Ø diameter in cm ± SD]	4.3 ± 1.1	4.5 ± 1.1	0.054
Duration of surgery [Ø in mins ± SD]	107 ± 49	120 ± 54	**0.043**
Hospital stay [Ø in days ± SD]	9.3 ± 4.9	9.2 ± 6.4	0.893

4. dataset of only **meningiomas** (16 patients)

Table A 4. Meningioma patients only (16 patients)

	nTMS group (n=16)	best match (n=16)	p-value
Age [y] (M ± SD)	58.4 ± 16.1	59.1 ± 14.9	0.886
Sex			
Female	9 (56.3%)	7 (43.7%)	0.476
Male	7 (43.7%)	9 (56.3%)	
Preoperative motor function			
No paresis	12 (75.0%)	10 (62.5%)	0.333
Mild paresis	3 (18.8%)	5 (31.3%)	
Severe paresis	1 (6.25%)	1 (6.25%)	
BMRC (M ± SD)	4.7 ± 0.6	4.6 ± 0.6	0.333
Location			
Frontal	10 (62.5%)	11 (68.8%)	0.709
Parietal	6 (37.5%)	5 (31.3%)	
Lesion size			
Diameter [Ø in cm]	3.5 ± 1.6	2.9 ± 1.3	**0.028**
Volume [cm³]	28.1 ± 24.0	18.4 ± 22.4	0.127
Postoperative motor function			
POD 7 BMRC (M ± SD)	4.1 ± 1.2	4.1 ± 1.3	1.000
POD 60 BMRC (M ± SD)	4.8 ± 0.5	4.9 ± 0.3	0.432
Improved	4 (25.0% of 16 100% of 4)	6 (37.5% of 16 100.0% of 6)	n.c.
Unchanged	10 (62.5%)	9 (56.3%)	0.718
Deteriorated	2 (12.5%)	1 (6.25%)	0.542
Surgery-related paresis			
None	11 (68.8%)	13 (81.3%)	0.409
Transient paresis	3 (18.8%)	2 (12.5%)	0.625
Permanent paresis	2 (12.5%)	1 (6.25%)	0.542
Gross total resection	16 (100.0%)	14 (87.5%)	0.131
Craniotomy size [Ø diameter in cm ± SD]	5.4 ± 1.2	5.5 ± 1.7	0.856
Duration of surgery [Ø in mins ± SD]	133 ± 57	156 ± 82	0.324
Hospital stay [Ø in days ± SD]	8.2 ± 3.6	8.2 ± 2.5	0.951

5. dataset of only **cavernomas** (6 patients)

Table A 5. Cavernoma patients only (6 patients)

	nTMS group (n=6)	best match (n=6)	p-value
Age [y] (M ± SD)	42.7 ± 16.4	38.7 ± 17.1	0.605
Sex			
Female	3 (50.0%)	1 (16.7%)	0.190
Male	3 (50.0%)	5 (83.3%)	
Preoperative motor function			
No paresis	4 (66.7%)	5 (83.3%)	0.695
Mild paresis	1 (16.7%)	0 (37.0%)	
Severe paresis	1 (16.7%)	1 (16.7%)	
BMRC (M ± SD)	4.5 ± 0.8	4.7 ± 0.8	0.695
Location			
Frontal	3 (50.0%)	2 (33.3%)	0.552
Parietal	3 (50.0%)	4 (66.7%)	
Lesion size			
Diameter [Ø in cm]	1.4 ± 0.5	1.9 ± 1.2	0.182
Volume [cm^3]	2.1 ± 1.9	2.8 ± 2.7	0.291
Postoperative motor function			
POD 7 BMRC (M ± SD)	4.5 ± 0.8	4.7 ± 0.5	0.695
POD 60 BMRC (M ± SD)	4.8 ± 0.4	4.8 ± 0.4	1.000
Improved	2 (33.3% of 6 100% of 2)	1 (16.7% of 6 100.0% of 1)	n.c.
Unchanged	4 (66.7%)	4 (66.7%)	
Deteriorated	0 (0%)	1 (16.7%)	
Surgery-related paresis			
None	6 (100%)	5 (83.3%)	n.c.
Transient paresis	0 (0%)	1 (16.7%)	
Permanent paresis	0 (0%)	1 (16.7%)	
Gross total resection	5 (83.3%)	6 (100%)	0.273
Craniotomy size [Ø diameter in cm ± SD]	3.9 ± 0.3	4.2 ± 0.6	0.263
Duration of surgery [Ø in mins ± SD]	132 ± 71	157 ± 31	0.554
Hospital stay [Ø in days ± SD]	8.2 ± 4.1	7.5 ± 2.8	0.793

The patient numbers for cavernoma are so small to preclude realistic statistical evaluation. They are only given to illustrate the general tendency of this subgroup.

12. Publications

Original manuscripts related to this thesis

a) Hendrix P, **Dzierma Y**, Burkhardt BW, Simgen A, Wagenpfeil G, Griessenauer CJ, Oertel J. Preoperative navigated transcranial magnetic stimulation improves gross total resection rates in patients with motor eloquent high-grade gliomas: A matched cohort study. *Neurosurgery*, 2020 Dec 8;nyaa486. doi: 10.1093/neuros/nyaa486, online ahead of print

b) **Dzierma Y***, Schuermann M*, Melchior P, Nuesken F, Oertel J, Rübe C, Hendrix P (*joint first authors). Optimizing adjuvant stereotactic radiotherapy of motor-eloquent brain metastases: sparing the nTMS-defined motor cortex and the hippocampus. *Frontiers in Oncology*, accepted 06-Jan-2021, doi: 10.3389/fonc.2021.628007

Conference proceedings

Schürmann M, **Dzierma Y**, Melchior P, Hendrix Ph, Nüsken F, Rübe Ch. (2020) Die Integration der navigierten transkraniellen Magnetstimulation in die Bestrahlungsplanung bei Hinrmetastasen – eine Planungsstudie zur Schonung des Motorkortex. Poster bei der 51. Jahrestagung der Deutschen Gesellschaft für Medizinische Physik (DGMP), 09.-12.09.20 – virtuell

Acknowledgements

First of all, thank you so much to Prof. Dr. med. Oertel for giving me the chance of working on this fascinating topic as my MD thesis. Thank you for your guidance, for showing me so much in the operating theatre, and for letting me take part in the many interesting conferences and hands-on-workshops.

I would also like to express my warmest thanks to my supervisor PD Dr. med. Philipp Hendrix for his extra-ordinary support and commitment. I fully appreciate his enthusiasm for this and the related studies, and his openness for including new topics such as radiotherapy planning. Thank you also for the opportunity to attend the Nexstim workshop in Munich, which gave me a much better idea of what the procedure looks like in real life.

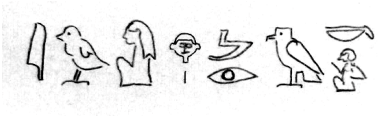
To all of the neurosurgical team, thank you for the warm welcome, and for many interesting insights in the neurosurgical operating theatre, hospital ward and intensive care unit.

I am deeply grateful to Prof. Dr. med. Rübe for his ongoing support and guidance ever since I started working in the Radiotherapy Department in 2011. Thank you for making my medical studies possible, and for giving me the flexibility to keep working alongside. Also, I appreciate the suggestion to pursue a medical doctorate – without you, I would have missed out on a great experience and some fascinating new projects!

I am thankful to all my colleagues who have been working with me in the different radiotherapy projects, in particular to Michaela Schürmann and Dr. rer. nat. Hendrik Auerbach for their enthusiasm for nTMS-based radiotherapy planning. Thank you also to Dr. med. Patrick Melchior, without whose competence and commitment none of the radiotherapy applications would have been possible. But more than this, I thank all of you for your friendship and for the wonderful working atmosphere.

Thank you to my family and friends for again putting up with me, with my lack of time, and with my endless talking about nTMS, and of course for taking my mind off the subject and enjoying your company. In particular, thank you to my father Paul for again proof-reading a thesis of mine with his usual interest and diligence.

Finally, a large thank you to my husband, for his patience, support, and love, and for being just the way he is.



Mein herzlicher Dank gilt dem Verein der Freunde des UKS für die Verleihung des Forschungspreises 2020 an Herrn PD Dr. Hendrix und mich für die Fortführung der begonnenen Studien im Projekt „Integration der navigierten transkraniellen Magnetstimulation und Traktographie in die Resektion und Strahlentherapie von motor-eloquenten malignen Hirntumoren: Einfluss auf die motorische und kognitive Funktion und Lebensqualität“.

Curriculum Vitae

Aus datenschutzrechtlichen Gründen wird der Lebenslauf in der elektronischen Fassung der Dissertation nicht veröffentlicht.

Eidesstattliche Erklärung

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Die aus anderen Quellen direkt oder indirekt übernommenen Daten und Konzepte sind unter Angabe der Quelle gekennzeichnet.

Bei der Auswahl und Auswertung folgenden Materials haben mir die nachstehend aufgeführten Personen in der jeweils beschriebenen Weise unentgeltlich geholfen:

1. Herr PD Dr. med. Philipp Hendrix, Klinik für Neurochirurgie des UKS hat mir das interessante Thema überlassen und mich fachlich angeleitet. Er hat die ursprüngliche Liste der nTMS-Patienten zur Verfügung gestellt und hat mir gezeigt, wie die Daten aus dem SAP und PACS erhoben werden konnten. Bei allen Unklarheiten stand er für Rückfragen zur Verfügung. Er hat sowohl den Chart Review, die Datensichtung, Auswertung und Interpretation supervidiert. Er hat das Manuskript für die Veröffentlichung in Neurosurgery geschrieben und Hinweise zum Erstellen dieser Dissertation gegeben.

2. Herr PD Dr. med. A. Simgen, Klinik für diagnostische und interventionelle Neuroradiologie des UKS hat die prä- und postoperativen MRT-Datensätze ausgewertet und die von mir bestimmten Tumor- und Ödem-Durchmesser, Tumorlokalisation, Vollständigkeit der Resektion und Rezidiv-Auftreten überprüft und korrigiert.

3. Frau Dr. G. Wagenpfeil, Institut für Medizinische Biometrie, Epidemiologie und Medizinische Informatik, hat bei der Auswahl der statistischen Tests, insbes. McNemar und McNemar-Bowker, und bei der Überlebensanalyse beraten, Rechnungen durchgeführt sowie überprüft. Der Bootstrap-Test war meine Idee.

4. Herr Dr. med. P. Melchior hat die strahlentherapeutischen Anwendungen supervidiert, Konturen für den Motor-Kortex, Hippocampus, Basalganglien und fehlende Risikoorgane erstellt, mir die Konturierung gezeigt und die von mir erstellten Konturen geprüft und korrigiert.

5. Frau Dipl.-Phys. Michaela Schürmann hat nach meiner Anleitung Bestrahlungspläne für die Strahlentherapie von Patienten mit und ohne Schonung des Motor-Kortex und des Hippocampus erstellt und dosimetrisch ausgewertet.

Allen genannten Personen möchte ich an dieser Stelle noch einmal meinen herzlichen Dank aussprechen.

Weitere Personen waren an der inhaltlich-materiellen Erstellung der vorliegenden Arbeit nicht beteiligt. Insbesondere habe ich nicht die entgeltliche Hilfe von Vermittlungs- bzw. Beratungsdiensten (Promotionsberaterinnen/Promotionsberater oder anderer Personen) in Anspruch genommen. Niemand hat von mir unmittelbar

oder mittelbar geldwerte Leistungen für Arbeiten erhalten, die im Zusammenhang mit dem Inhalt der vorgelegten Dissertation stehen.

Die Arbeit wurde bisher weder im Inland noch im Ausland in gleicher oder ähnlicher Form in einem anderen Verfahren zur Erlangung des Doktorgrades einer anderen Prüfungsbehörde vorgelegt.

Ich versichere an Eides statt, dass ich nach bestem Wissen die Wahrheit gesagt und nichts verschwiegen habe.

Die Bedeutung der eidesstattlichen Erklärung und die strafrechtlichen Folgen einer unrichtigen oder unvollständigen eidesstattlichen Erklärung sind mir bekannt.

Homburg, 10.01.2021