Cost-effectiveness of preoperative motor mapping with navigated transcranial magnetic brain stimulation in patients with high-grade glioma

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OBJECTIVE Navigated transcranial magnetic stimulation (nTMS) is used to identify the motor cortex prior to surgery. Yet, there has, until now, been no published evidence on the economic impact of nTMS. This study aims to analyze the cost-effectiveness of nTMS, evaluating the incremental costs of nTMS motor mapping per additional quality-adjusted life year (QALY). By doing so, this study also provides a model allowing for future analysis of general cost-effectiveness of new neuro-oncological treatment options.

METHODS The authors used a microsimulation model based on their cohort population sampled for 1000 patients over the time horizon of 2 years. A health care provider perspective was used to assemble direct costs of total treatment. Transition probabilities and health utilities were based on published literature. Effects were stated in QALYs and established for health state subgroups.

RESULTS In all scenarios, preoperative mapping was considered cost-effective with a willingness-to-pay threshold < 3*per capita GDP (gross domestic product). The incremental cost-effectiveness ratio (ICER) of nTMS versus no nTMS was 45,086 Euros/QALY. Sensitivity analyses showed robust results with a high impact of total treatment costs and utility of progression-free survival. Comparing the incremental costs caused by nTMS implementation only, the ICER decreased to 1967 Euros/QALY.

CONCLUSIONS Motor mapping prior to surgery provides a cost-effective tool to improve the clinical outcome and overall survival of high-grade glioma patients in a resource-limited setting. Moreover, the model used in this study can be used in the future to analyze new treatment options in neuro-oncology in terms of their general cost-effectiveness.

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KEYWORDS cost-effectiveness; high-grade glioma; motor mapping; nTMS

WORLD Health Organization (WHO) grade III and IV gliomas are malignant tumors of the brain and represent the majority of primary brain tumors developing from glial cells. Although no curative treatment is yet known, advances in neuro-oncological treatment nowadays include a multimodal concept of therapy: cytoreductive surgery followed by combined radiotherapy (RTx) and chemotherapy (CTx) using temozolomide (TMZ).

Many studies have found a significant correlation between the extent of resection (EOR) and the overall survival (OS) of patients with these tumors, and extensive resection remains, whenever possible, the gold standard.^{13,14,22} This standard approach can be enhanced by several pre- and intraoperative tools, such as neuronavigation, intraoperative neuromonitoring, 5-aminolevulinic acid (5-ALA), and motor/language mapping prior to surgical removal of eloquent tumors.

ABBREVIATIONS 5-ALA = 5-aminolevulinic acid; CEAC = cost-effectiveness acceptability curve; CHOICE = CHOosing Interventions that are Cost-Effective; CR = complete resection; CTx = chemotherapy; EOR = extent of resection; fMRI = functional magnetic resonance imaging; GBD = Global Burden of Disease Study; GDP = gross domestic product; GTR = gross-total resection; HGG = high-grade glioma; ICER = incremental cost-effectiveness ratio; MEG = magnetoencephalography; nTMS = navigated transcranial magnetic stimulation; OS = overall survival; PFS = progression-free survival; PR = partial resection; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; RTx = radiotherapy; TMZ = temozolomide; WHO = World Health Organization; WTP = willingness-to-pay; YLD = years lived with disability; YLL = years of life lost.

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The current gold standard for postresection treatment of patients with newly diagnosed high-grade gliomas (HGGs) includes adjuvant therapy with concomitant radiotherapy and chemotherapy with TMZ, followed by chemotherapy alone (Stupp protocol). Despite the extensive multimodal treatment, the mean survival is limited. One reason is the challenging identification of tumor margins in locations close to highly eloquent areas, which makes it difficult to achieve complete resection.²¹

In addition to imaging techniques such as functional magnetic resonance imaging (fMRI), navigated transcranial magnetic stimulation (nTMS) can be used to identify eloquent cortex noninvasively. It was even shown that preoperative nTMS improves the EOR²³ and the clinical outcome.^{12,13} Based on the principle of electromagnetic induction, we can identify the cortical representation of the motor cortex by measuring motor evoked potentials from a specific area of the brain. Recent studies have shown that nTMS is superior to other noninvasive techniques, such as fMRI and magnetoencephalography (MEG).²³ It was therefore recently reported to be the most reliable preoperative mapping option for neuro-oncological centers if providing state-of-the-art care.²⁰

Nowadays, health care providers and consumers benefit from scientific progress but also face multiple challenges, including a surplus of treatment options conflicting with evidence-based therapy regimens; a rapidly changing industry and patient population; and of course, increasing health care expenses and financial boundaries.

Only a few publications have considered the economic impact implied by the clinical benefits of alternative treatment options and optimizations. Published articles have analyzed the economic benefit of 5-ALA for intraoperative tumor resection and the financial outcome of carmustine implants as well as intraoperative neurophysiological monitoring.^{8,10,11,21} To our knowledge, no study has been conducted on the economic evaluation of nTMS for preoperative motor mapping. Thus, the aim of this study is to estimate the financial burden of disease and the cost-effectiveness of nTMS for HGG patients.

This study also provides a model that can be used in the future to analyze any new treatment option in neuro-oncology in terms of its general cost-effectiveness.

Methods

Patients

We included cohort patients in our simulation model, based on adults older than 18 years with histologically diagnosed HGG (WHO grades III and IV) who underwent surgical and adjuvant therapy in Germany in our university hospital following standard clinical practice (Table 1). We simulated several clinical scenarios for the treatment option (with nTMS) and the comparator cohort (no nTMS):

1. EOR: gross-total resection (GTR) versus partial resection (PR)
2. Motor deficits (no vs present deficits)
3. At each stage, the corresponding probability of death was included

The probabilities of complete resection (CR) and PR

TABLE 1. Utility values

Health State	Value	Reference	Variation for PSA
uProgressionFree_nodeficit	0.8872	Garside et al., 2007	0–1
uRTx_CTx	0.7426	Garside et al., 2007	0–1
U_TMZ_nodeficit	0.7314	Garside et al., 2007	0–1
u_motoricdeficit	0.381	Murray et al., 1994*	0–1

Utility values (u) for different health states used for the simulation, as well as variation range for probabilistic sensitivity analysis (PSA) for the case of radiotherapy (RTx) and chemotherapy (CTx) with TMZ.

* GBD 1990.

for patients who underwent nTMS and for the control group, as well as the probability of death, were extracted from previously published results from our study group.¹³

Clinical Outcome

Different clinical outcomes were included in our model in order to differentiate between years of life lost (YLL) and years lived with disability (YLD) due to mild and severe motor deficits. The outcome units were evaluated in quality-adjusted life years (QALYs):

$$\sum_{i=0}^1 y(i) * u(i)$$

= sum of life years spent in the lifespan i * utility during the life period i .

Utilities for each stage of treatment were extracted from the Global Burden of Disease Study (GBD 1990),¹⁸ and from previously published literature^{8,10,19,25} (Table 1). A discount rate of 3% was applied to health outcomes, as recommended by the WHO CHOICE (CHOosing Interventions that are Cost-Effective) guidelines.

Medical Costs

Table 2 summarizes the costs included in our evaluation. The costs of each scenario were estimated from a health care system perspective, not including any indirect costs. The costs were estimated according to the following treatment strategy:

- Operation and hospital inpatient stay (with and without performance of nTMS)
- Combined adjuvant therapy: focal RTx (6 weeks, 5 days a week with a fraction of 2 Gy per day) + CTx with an alkylating agent (TMZ 75 mg/m² per day)
- Adjuvant TMZ therapy after RTx: 1st week 300 mg for 5 days, then 5 cycles of 5 days of 400 mg/dose daily
- In case of tumor recurrence: adjuvant CTx with TMZ: 6 cycles of 400 mg/day for 5 days a week

To calculate the average dosages of TMZ, we assumed a typical patient's body surface of approximately 2 m², leading to an initial dosage of 150 mg TMZ for the concomitant TMZ therapy.

Model Structure

We constructed a decision tree–based simulation mod-

Costs included in the simulation model, classified by category, unit cost, total cost, and variation range used for sensitivity analysis (PSA).

We used repeated random sampling to more accurately reflect our probability distributions. The time horizon included the lifespan of 2 years, therefore opting for the possibility of a second period of CTx with TMZ. Alternative treatment options, such as alkylating agents (carmustine/lomustine), VEGFR and EGFR inhibitors (bevacizumab/cetuximab), or other multitargeted drugs, were not included.¹⁷ A hypothetical cohort, with similar clinical and demographic properties as the patients in our previously

Prior to surgery, patients would receive either of 2 competing preoperative imaging techniques, dividing the population in 2 groups of interest: one group would receive standard preoperative MRI, which would then be used for intraoperative neuronavigation to localize the motor cortex, while the other group would undergo mapping with nTMS to identify the motor cortex in addition to undergoing the standard preoperative MRI and intraoperative neuronavigation. After the surgical procedure, clinical outcome was assessed and the EOR was measured based on postoperative MRI scans.

We considered 3 different health outcomes (no motor

TABLE 3. Patient data

Characteristic	nTMS	No nTMS
Mean age (yrs)	58 ± 13.8	60.3 ± 14.7
Sex: male (%)	64.3	64.3
Preop KPS (%)	80	80
Preop paresis: severe (%)	7.1	2.9
GTR (%)	65.7	45.7
New motor paresis (%)		
After GTR	17.4	28.1
After PR	12.5	34.2

KPS = Karnofsky Performance Status.

Patient data and percentage of patients with and without new permanent paresis after GTR and PR according to postoperative MRI, based on Krieg et al., 2015.¹³

deficit, permanent severe paresis [motor deficit $\leq$ grade 3 for the chosen time period], and death) as well as 2 resection rates, GTR and PR, resulting in different clinical outcomes and recurrence risks. From this stage on, each patient can have different clinical courses: progression-free survival (PFS), tumor recurrence (or progress), and/or death. These 3 stages were considered end stages, and costs and utilities were analyzed at each of the end branches of our decision tree.

Transition parameters and proportions were again extracted from previously published literature and entered into the model with a specific statistical distribution.^{8,10,13,19}

Utilities were estimated and adjusted for adjuvant therapy (RTx and concomitant TMZ) after the operation (uRTx_CTx), recurrent tumor chemotherapy (U_TMZ_noddeficit), a postoperative permanent deficit (u_motoricdefi-

cit), and PFS (uProgressionFree_noddeficit). The utilities for each health state are described in Table 1 and estimated from the GBD as well as previously published data comparing cost-efficiencies in intracranial tumor patients.

Transition Probabilities

In order to account for the uncertainty across our different parameters, we added statistical distributions to the decision tree. Table 4 shows the different transition probabilities and their assigned distributions entered into our model. Transition probabilities, such as the rate of GTR, rate of PR, and clinical outcomes, were assigned to beta distributions, a continuous probability distribution having 2 parameters most commonly used to model one's uncertainty about the probability of success.

The probability of death was confined to a lognormal distribution, and tumor progression/recurrence was assigned to an exponential function. The specific values and their standard deviations, as well as the assigned distributions, were obtained from previously published literature and are described in Table 5.^{9,10,13,25}

Probabilistic Sensitivity Analysis

To consider all occurring uncertainties across our data, and in order to understand and estimate the impact of different variables on our results, we used decision tree probabilities and utilities using random sampling simulation techniques,^{6,7} a stochastic method based on the random sampling of inputs. Estimated variables are repeatedly sampled to determine an empirical distribution for decision-makers.²

Sensitivity analysis quantifies and qualifies the uncertainty underlying the decision process for decision-makers in health care policy.¹ Probabilistic sensitivity analysis

TABLE 4. Probability distributions

Type	Name	Description
Beta	p_GTR_nTMS	Probability of GTR w/ nTMS
Beta	p_PR_nTMS	Probability of PR w/ nTMS
Lognormal	p_Death_nTMS	Probability of death w/in 3 mos w/ nTMS
Beta	p_GTR_nonTMS	Probability of GTR w/o nTMS
Beta	p_PR_nonTMS	Probability of PR w/o nTMS
Lognormal	p_death_nonTMS	Probability of death w/in 3 mos w/o nTMS
Beta	p_noddeficit_nTMS_GTR	Probability of no deficit w/ GTR & nTMS
Beta	p_deficit_nTMS_PR	Probability of deficit w/ PR & nTMS
Beta	p_deficit_nonTMS_PR	Probability of deficit w/ PR w/o nTMS
Beta	p_noddeficit_nonTMS_GTR	Probability no deficit w/ GTR w/o nTMS
Beta	p_deficit_nTMS_GTR	Probability of deficit w/ GTR & nTMS
Beta	p_deficit_nonTMS_GTR	Probability of deficit w/ GTR w/o nTMS
Beta	p_noddeficit_nTMS_PR	Probability of no deficit w/ PR & nTMS
Beta	p_noddeficit_nonTMS_PR	Probability of no deficit w/ PR w/o nTMS
Lognormal	p_Death_GTR_nTMS_noddeficit	Probability of death for GTR w/ nTMS
Exponential	p_progress_GTR	Probability of tumor recurrence for GTR
Exponential	p_progress_PR	Probability of tumor recurrence for PR

Description of probability distributions included in our decision model, based on the transition probability extracted from previously published data.

TABLE 5. Simulation model variables

Type	Name	Description (probability of)	Value	Source
Beta	p_GTR_nTMS	GTR w/ nTMS	0.6255	Krieg et al., 2015
Beta	p_PR_nTMS	PR w/ nTMS	0.3115	Krieg et al., 2015
Lognormal	p_Death_nTMS	Death w/in 3 mos w/ nTMS	0.063	Krieg et al., 2015 (2)
Beta	p_GTR_nonTMS	GTR w/o nTMS	0.362	Krieg et al., 2015
Beta	p_PR_nonTMS	PR w/o nTMS	0.448	Krieg et al., 2015
Lognormal	p_death_nonTMS	Death w/in 3 mos w/o nTMS	0.19	Krieg et al., 2015 (2)
Beta	p_nodeficit_nTMS_GTR	No deficit w/ GTR & nTMS	0.871	Krieg et al., 2015 (6)
Beta	p_nodeficit_nTMS_PR	No deficit w/ PR & nTMS	0.867	Krieg et al., 2015 (6)
Beta	p_nodeficit_nonTMS_GTR	No deficit w/ GTR w/o nTMS	0.833	Krieg et al., 2015 (6)
Beta	p_nodeficit_nonTMS_PR	No deficit w/ PR w/o nTMS	0.637	Krieg et al., 2015 (6)
Beta	p_deficit_nTMS_GTR	Deficit w/ GTR & nTMS	0.129	Krieg et al., 2015 (6)
Beta	p_deficit_nTMS_PR	Deficit w/ PR & nTMS	0.133	Krieg et al., 2015 (6)
Exponential	p_progress_GTR	Progress for GTR	0.0197	Esteves et al., 2015 (7)
Exponential	p_progress_PR	Progress for PR	0.0086	Esteves et al., 2015 (7)

Distribution values and types included in the simulation model and sources used to extract the data.

(PSA) assigns probability distributions to input values and simulates different scenarios to estimate the overall extent of influence of variables on the overall outcome, such as, in our case, the incremental cost-effectiveness ratio (ICER). Results can be presented in a tornado diagram, listing the different variables by decreasing relative importance for the outcome based on low/median and high values.

The willingness-to-pay (WTP) was set at 3*per capita gross domestic product (GDP) (35,810.07 Euros, Germany 2014), following WHO CHOICE (CHOosing Interventions that are Cost-Effective) guidelines for policy makers in health economics. ICER values < 1 per capita GDP were considered very cost-effective. An ICER value over 3*per capita GDP was above the cost-effectiveness threshold.

Perspective

The analysis was conducted from a health insurer perspective, aiming to include health benefits with smallest possible growth in costs. It reflects the direct treatment costs and is influenced by the length of hospital stay and rates of complications, such as additional treatments and operations. Indirect costs, such as loss of productivity and further treatment options, such as physiotherapy/ergotherapy/rehabilitation, were not included, and therefore the analysis missed the additional costs of burden of disease after the inpatient period.

Results

Base-Case Analysis

The mean total direct costs per glioma patient, including costs for hospital inpatient days, operation, and adjuvant treatment (Stupp), with and without nTMS were 61,267 and 62,214 Euros, respectively. Further CTx in case of a tumor recurrence added an additional cost of 15,640 Euros (equal to 6 cycles of TMZ). On average, patients who undergo preoperative mapping spent fewer days as hospital inpa-

tients compared to the control group without mapping (12 vs 15 days). Table 6 presents the total costs of treatment.

The mean effectiveness amounted to 0.55 QALY, compared to 0.37 QALY without nTMS. This represents an increase of 0.18 QALY. Figure 2 displays the average pay-offs for each strategy, obtained by rolling back the decision tree.

Incremental Cost-Effectiveness Ratio

Table 6 shows the results of 1000 repeated samplings using random sampling simulation. The mean additional cost for nTMS was 7969 Euros; incremental effectiveness amounted to 0.18 QALY. For the average patient, the base-case incremental cost-effectiveness ratio (ICER) was 45,086 Euros/QALY gained (therefore being cost-effective according to the WHO CHOICE guidelines). Considering the indirect costs not included in our analysis, the ICER for a societal perspective would be much lower because of inclusion of the loss of productivity due to motor deficits. Compared to other treatments, nTMS offers a cost-effective preoperative tool for use in treating glioma patients, and should therefore be routinely applied for every patient with a tumor in an eloquent area of the brain.

Uncertainty Analyses

To determine the uncertainty surrounding cost-effectiveness, we first used 1-way sensitivity analysis.

Figure 3 describes the cost-effectiveness acceptability curve (CEAC), plotting the WTP (x-axis) versus the probability of cost-effectiveness of nTMS. We used a maximum WTP of 3*per capita GDP (= 107,430 Euros) according to WHO CHOICE guidelines. The cost-effectiveness scatterplot shows the uncertainty around our ICER values. Each dot represents 1 cost-effectiveness pair from the simulation results (n = 1000).

We found that our model is particularly sensitive to variations in quality of life during PFS and to the cost of

TABLE 6. Cost-effectiveness statistics

Parameter	nTMS	no nTMS
Costs (Euros)		
Mean	51,976.56	44,007.10
SD	503.82	640.63
Minimum	50,207.07	41,813.87
2.5%	50,988.93	42,774.97
10%	51,341.53	43,218.21
Median	51,976.90	43,972.95
90%	52,600.96	44,862.15
97.5%	52,972.13	45,211.55
Sum	51,976,558.70	44,007,099.47
Size (n)	1000	1000
Variance	253,832.66	410,405.21
Effects (QALY)		
Mean	0.55	0.37
SD	0.02	0.02
Minimum	0.46	0.32
2.5%	0.49	0.34
10%	0.52	0.35
Median	0.55	0.37
90%	0.58	0.39
97.5%	0.59	0.40
Sum	550.61	373.85
Size (n)	1000	1000
Variance	0.00	0.00

Random sampling simulation cost-effectiveness statistics showing the results of 1000 samplings for subjects with nTMS and without. Mean incremental costs were 7969 Euros, mean incremental effects 0.18 QALY.

TMZ (which is not surprising, as it represents the greatest contribution to overall treatment costs). Other factors, such as cost per day of hospitalization and cost of nTMS, had only little impact on the mean ICER value (Fig. 4).

Perspectives

Regarding the health-economical perspectives described previously, nTMS provides benefits on each level. From a health care provider perspective, it reduces the length of hospital stay and costs associated with perioperative complications, and it increases the GTR rate.

From a health insurer perspective, as examined in our study, nTMS is comparable to an investment in future health, as it decreases the rate of postoperative paresis and direct treatment costs.

The larger the scale, the higher appears to be the benefit of nTMS: from a societal perspective, the costs saved are increased by the proportion of indirect costs, including rehabilitation, physiotherapy, and productivity loss due to occupational disability.

Discussion

General Aspects

We conducted a cost-effectiveness analysis of imple-

mentation of nTMS for preoperative motor mapping versus the gold standard (MRI) in glioma patients. We constructed a decision tree model and used random sampling simulation for dealing with uncertainty around our parameter values. The expected ICER value per gained QALY was around 45,000 Euros, therefore cost-effective and below the WTP following the WHO CHOICE guidelines. Sensitivity analyses suggested a high impact of health utility and costs of TMZ on the expected ICER value.

Special Considerations of the Model

Since its implementation, nTMS has been increasingly gaining importance in the clinical setting. On average, the incremental costs per TMS patients are only 842 Euros. Meanwhile, the high ICERs result not only from the incremental costs per case, but mainly from the overall survival and therefore additional costs for chemotherapy (main share of total costs). Adding more life years means adding more costs for the overall treatment. If only direct incremental treatment costs are compared (as previously done by Slof et al. for the case of 5-ALA fluorescence, resulting in an ICER of 9021 Euros per QALY²¹), the costs of nTMS per patient decrease to 1967 Euros per QALY gained, meaning that it is very cost-effective (< per capita GDP). Esteves et al. included costs of therapy such as chemotherapy and variables such as stable disease and tumor recurrence and found an ICER of 13,000 Euros per QALY gained.⁸ We did not compare nTMS to other additional therapies, as 5-ALA was given to all patients and fMRI is not performed in our department.

In addition to the overestimated costs, the time horizon used (2 years) puts a strong restriction on the possible effects and thereby underestimates the benefits of nTMS. Life years gained, having a high impact on total QALYs gained, are not entirely included in our analysis. We expect that gathering more long-term data and expanding the time horizon to 5 years will decrease the average costs per QALY gained by increasing the effectiveness in terms of overall survival.

A further restriction of our presented model involves the population data used: the input data are provided by previous studies conducted in our department and may not reflect the reality in other clinical departments; thus, we would like to use a broader study population in the future as studies including the nTMS modality improve over time and include more and more patient numbers.

Many factors have not been included in our simulation model. Examples are operation or RTx for recurrent tumors, methylation status, and alternative treatments (carmustine, receptor inhibitors), as well as costs for postoperative physiotherapy, cost of caregivers in case of persistent disability, and the loss of productivity caused by unemployment and YLL (indirect costs).

A highly influential cost factor has been neglected in our model but will be included in further research: HGGs are extremely aggressive tumors, and the vast majority of patients have tumor recurrence despite intensive treatment. The costs of recurrent tumor resections have not been considered, although a prospective study showed that 1 year after diagnosis approximately 15% of patients with histo-

FIG. 2. Costs and effects per selected scenario for both groups: patients undergoing nTMS preoperatively and patients without motoric mapping. nTMS increases the overall effectiveness by 0.18 QALY.

FIG. 3. A: Cost-effectiveness acceptability curve (CEAC) of preoperative nTMS treatment. The willingness-to-pay is set at 3*per capita GDP (107,430 Euros). The 2 lines intersect when WTP is equal to the ICER. **B:** Scatterplot distributions of ICER distribution for 1000 samplings, disclosing the variability within the original study sample.

logically confirmed glioblastoma had undergone resection for recurrence, and at 2 years after diagnosis the rate was approximately 30%.³

In health economics, several perspectives can be adopted while conducting cost-effectiveness analyses. In this study, we used data from a health insurance point of view, accounting for direct treatment costs and health benefits measured in QALYs. If a societal perspective is adopted (maximizing societal health, decreasing overall spending), all occurring costs related to an illness have to be included. Indirect costs in particular play a pivotal role in current economies. A study conducted in Sweden by Blomqvist et al. showed that indirect costs amount to 75% of the total cost of illness for malignant glioma patients, mainly due to early mortality.⁴ Excluding indirect costs may underestimate the cost-saving aspects of new treatment techniques, such as nTMS.

In this study, we only included HGG patients, and we excluded patients with other tumors, such as metastases, in eloquent areas of the brain. While trying to standardize tumor patients with brain metastases, we face more difficulties caused by differing life expectancies, tumor recurrence probabilities, and systemic chemotherapy treatment, leading to more subgroups than in glioma patients and nonfeasible generalization. Still, by adapting the model to more subtle assumptions, cost-effectiveness analyses could be conducted for patients with all kinds of intracranial tumors.

Sensitivity analyses revealed a high impact of health utilities on the expected ICER. In our case, utility values used were obtained from previously published studies. No prospective investigation of health preference has been conducted, and especially for the case of motoric deficits (corresponding to a utility of 0.381), we lack evidence-based utilities properly reflecting health choices. With the increasing use of QALYs in health care decision-making, there is a strong need for more reliable preference weights,

and further research needs to focus and to be conducted on health-related utilities.^{16,24}

Many indirect beneficial aspects of nTMS have not been included in our analysis. Litofsky et al. reported in 2004 that depression is a common complication after surgical treatment of HGGs.¹⁵ In addition to the benefits in clinical outcome, nTMS increases patient satisfaction, increasing their understanding of pathology and surgery, and decreasing their anxiety level (Senger et al., unpublished presentation) and may increase their quality of life. Furthermore, a factor not included in our model is the improved quality of life related to a GTR itself. Brown et al. found a significant association between GTR and the experienced health utility after the operation.⁵

Meanwhile, a model is only as good as its assumptions. Most data and units used in this model were prospectively collected but based on nonrandomized studies using historical controls. Working toward more reliable data will provide us the benefit of a more realistic simulation and more precise results.

The increased effectiveness of 0.18 QALY caused by nTMS is, in its outcome, comparable to the effectiveness of 5-ALA (0.16 QALY, reported by Esteves et al.⁸). Furthermore, the sensitivity analysis showed similar results regarding the impact of different variables on the overall outcome: progression-free utility had the highest influence on the ICER value.

As usual, new techniques need to find their way into clinical practice. This study demonstrates that nTMS motor mapping can provide a substantial economical benefit, thereby representing not only an improvement of medical treatment, but also a cost-effective tool for health insurance and society.

Conclusions

By using a cohort simulation model based on recently

FIG. 4. Tornado diagram presenting the influence of different variables listed by importance. The main impact was achieved by the utility of patients being progression free without any motoric deficit (= their quality of life), while inputs such as cost of nTMS and cost of operation had only little impact on the expected ICER value. EV = expected value.

published data, we evaluated the cost-effectiveness of pre-operative motor mapping for HGG patients. For an average patient, the incremental cost of 1 QALY is 45,000 Euros. The ICER is under the WTP threshold described by the WHO CHOICE guidelines and is therefore regarded as cost-effective. Focusing on the incremental costs of nTMS alone without the additional adjuvant treatment, the ICER was even considered “very cost-effective,” having a value of approximately 8000 Euros. This economic evaluation supports the significance and clinical relevance of nTMS in a preoperative setting and adds to its clinical benefits a financial sustainability.

Moreover, with this study we provide a model that can be used in the future to analyze new treatment options in neuro-oncology in terms of their general cost-effectiveness.

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Disclosures

BM and SMK report being consultants for Brainlab AG (Munich, Germany). SMK reports being a consultant for Nexstim Plc. (Helsinki, Finland).

Author Contributions

Conception and design: Krieg, Butenschön. Acquisition of data: Krieg, Butenschön, Ille, Sollmann. Analysis and interpretation of data: Krieg, Butenschön. Drafting the article: Krieg, Butenschön. Critically revising the article: Krieg, Ille, Sollmann. Reviewed submitted version of manuscript: Krieg, Ille, Sollmann, Meyer. Approved the final version of the manuscript on behalf of all authors: Krieg. Statistical analysis: Butenschön. Administrative/technical/material support: Krieg, Meyer. Study supervision: Krieg, Meyer.

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