תאריך:

הפקולטה לרפואה ע"ש סאקלר

הצעה לעבודת גמר בנושא:

**Characterization of intraoperative sub-cortical monitoring of various parts of the pyramidal tracts among patients with brain tumors located in the temporal lobe.**

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**Abstract:**

**Background:** Preserving motor function during surgical resection of intraaxial brain tumors has been a challenge for neurosurgeons for many years. Several techniques have been developed to achieve this goal, amongst which Intraoperative Stimulation Monitoring (ISM) is known for being an advanced technique for preserving motor function. As stated in previous literature, there is a linear correlation between the threshold level needed to elicit Subcortical Stimulated Minimal Electric Potential (scrtMEPs) and the distance from the corticospinal tracts (CSTs). Currently, there is no structured method which enables the differentiation between different regions of the pyramidal tract by means of neurophysiological monitoring.

**Objectives:** Characterize the unique electrophysiological signature of the cerebral peduncle as opposed to the internal capsule among patients with intraaxial temporal lobe tumors.

**Hypothesis:** We hypothesize that the electrophysiological motor response from the cerebral peduncle will be more condensed compared to a more scattered motor response from the internal capsule. In other words, subcortical stimulation adjacent to cerebral peduncle will affect more muscles compared to a more confined response from the internal capsule.

**Methods:** We will retrospectively analyze all the patients who underwent surgical resection of intraaxial temporal tumors adjacent to motor pathways, with electrophysiological mapping and monitoring, in the neurosurgery department at the Tel-Aviv Medical Center between 2016-2018. We will compare the electrophysiological characteristics between the motor responses from the cerebral peduncle and the motor response of the internal capsule.

**Importance of the study:** By means of this research we hope to achieve a better understanding of various aspects of the motor response during brain tumor surgery with ISM which will enable neurosurgeons to improve motor function preservation.

 **Keywords:** Intraoperative Stimulation Monitoring (ISM), Temporal tumors, Intraaxial tumors, corticospinal tracts (CSTs), Motor Pathways, Surgical outcome.

**תקציר:**

**רקע מדעי:** שימור התפקוד המוטורי במהלך ניתוחים לכריתת גידולים מוחיים, ובמיוחד גידולים הממוקמים באונה הטמפורלית, מהווה אתגר משמעותי. קיימות מספר טכניקות ניתוחיות, בהן ניתן להשתמש על מנת למנוע פגיעה מוטורית אפשרית, כאשר השיטה הנפוצה ברוב המרכזים הנוירוכירורגים בעולם הינה שיטה לניטור גירוי חשמלי בזמן ניתוח (ISM). כפי שתואר בספרות בעבר, קיים קשר לינארי בין סף הגירוי התת-קורטיקלי(scrtMEPs) הנדרש ליצירת תגובה מוטורית, לבין המרחק מהמסילות הקורטיקו-ספינאליות (CSTs). כיום, אין שיטה מקובלת שמסוגלת להבדיל בין אזורים שונים של המערכת הפירמידלית (PT) באמצעות ניטור נוירופיזיולוגי.

**מטרה :** אפיון החתימה האלקטרו-פיזיולוגית האופיינית ל- Internal capsule לעומת זו המאפיינת את ה-cerebral peduncle , בקרב מטופלים אשר עברו ניתוחים לכריתת גידולים מוחיים באונה הטמפורלית.

**השערה**: אנו משערים כי התגובה האלקטרופיזיולוגית מאזורים הקרובים ל- cerebral peduncle תהיה צפופה יותר בהשוואה לתגובה מוטורית יותר מפוזרת בקרבה ל- internal capsule. במילים אחרות, גירוי תוך מוחי באזור ה- cerebral peduncle יגרום לתגובה מוטורית של מספר גדול יותר של קבוצות שרירים ובאזורים מגוונים בגוף הנבדק לעומת תגובה מוגבלת יותר של פחות קבוצות שרירים לגירוי מאזור ה- internal capsule.

**שיטה:** המחקר מבוסס על אנליזה רטרוספקטיבית של חולים שעברו ניתוח להסרת גידולים מוחיים באונה הטמפורלית בקרבת אזורי תנועה תחת ניטור אלקטרו-פיזיולוגי בין השנים 2016-2018 במחלקה הנוירוכירורגית במרכז הרפואי תל-אביב. אנו נשווה את המאפיינים האלקטרופיזיולוגיים של התגובות המוטוריות לגירויים בקרבה ל- cerebral peduncle לעומת התגובות לגירויים ב- Internal capsule.

**חשיבות המחקר:** הבנת מאפייני התגובה המוטורית בתגובה לגירוי אלקטרופיזיולוגי באזורים שונים של המערכת הפירמידלית(PT) תאפשר שימור טוב יותר של תפקודים מוטורים במהלך ניתוחי מוח המבוצעים תחת ניטור גירוי חשמלי בזמן ניתוח (ISM).

**מילות מפתח:** ניטור גירוי חשמלי בזמן ניתוח (ISM), גידולים באונה בטמפורלית, גידולים מוחיים , המסילות הקורטיקו-ספינאליות (CSTs), מסילות מוטוריות, תוצאים ניתוחיים.

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# **Scientific Background**

Preserving motor function during surgical resection of intraaxial brain tumors has been a major challenge for many years. One of the possible explanations for this challenge is brain shift, which is affected by CSF loss, tumor resection, surgical retraction, and gravity [1], which limits the ability to predict the corticospinal tracts (CSTs) location through current intraoperative systems [2, 3]. Nowadays, this limitation has become a pressing issue, since there is a growing evidence that more extensive surgical resection may be associated with more favorable life expectancy for both patients with low-grade and high-grade gliomas [4, 5].

Surgery is the primary treatment for brain tumors that can be removed without causing severe damage. The purpose of brain-tumor resection is to maximize tumor removal while sparing healthy tissue. The extent of resection is a key prognostic factor; however, complete tumor resection is often not possible. Due to the imprecise correlation between pre-operative images and intraoperative anatomy as well as poor differentiation of low-grade glioma from normal tissue in non-eloquent areas, substantial tumor volume may remain postoperatively. The frequency of residual tumor following surgery is surprisingly high, leading to rapid disease recurrence [6].

Gliomas are the most frequent intrinsic tumors of the central nervous system [7]. The temporal lobe is a favored anatomic site for two common types of gliomas, Pleomorphic xanthoastrocytoma (PXA), that typically arises in a superficial cerebral location in children and young adults, and Oligodendrogliomas (OGs), most often present in Caucasian males in their fourth and fifth decades of life [8]. Temporal lobe tumors may cause impairments of visual fields (optic pathway), memory, comprehension, and behavior [9].

Despite all the current advances in glioma surgery, many neurosurgeons still believe that tumors involving certain areas, such as the primary motor cortex, and the corticospinal fibers that pass through the internal capsule and the cerebral peduncle, are unresectable due to their functional significance. It is thought that the risk of developing new or worsened motor deficits outweighs the benefit of surgery [10]. Therefore, when operating on nearby infiltrating tumors, the main purpose of intraoperative mapping (IOM) procedures is to reliably identify cortical areas and subcortical pathways involved in motor function, in addition to the preservation of sensory, language, and cognitive function. Although similar techniques are utilized, the application of mapping at different centers involves a diversity of approaches [3].

To localize critical brain structures and tumors, techniques such as Preoperative Functional Neuroimaging, Neuronavigation, Fluorescent Dyes, Magnetic Resonance Imaging (MRI) in surgical field, and Intraoperative Stimulation Mapping (ISM) have been used. Among the different approaches for Intraoperative brain mapping, ISM is the most reliable method to estimate the proximity to the CSTs during resection of deep-seated lesions in the white matter [11]. Meta-analysis of 90 reports published between 1990 and 2010 (including 8091 adult patients with supratentorial infiltrative gliomas) [5 - 12] found that the resection of Gliomas using ISM is associated with reduction in late severe neurologic deficits, two times greater than that with surgery without ISM, and with more extensive resection. Although this technique involves binary interpretation, that is the presence or absence of a motor response to the delivered subcortical stimulus at a constant intensity, this method is not accurate enough, given that the actual distance between the stimulated point and the CSTs cannot be quantified.

The threshold level needed to elicit Subcortical-Stimulated Minimal Electric Potentials (scrtMEPs) and the distance to the CSTs (based on DTI tractography), demonstrated a linear order, and a relationship of 0.97 mA for every 1 mm of brain tissue distance from the CSTs [2]. However, these assumptions are a matter of some debate because distributions of electrical charge and voltage in the brain generally do not show a linear decay, but instead show a nonlinear decay as a function of distance from the stimulation electrode [13].

The anisotropy or directionality of diffusion for different areas of specific white matter tracts can be quantified by scalar quantities such as fractional anisotropy (FA). The Average FAs obtained from the internal capsule are normally lower than those of the cerebral peduncle, due to the more condensed fibers organization of the latter [14]. This difference may influence the motor response recorded during electrical stimulation of each of those areas.

Through thoughtful pre- and intraoperative mapping and monitoring the extent of resection can be maximized, with low rates of surgery-related deficits. The available techniques are feasible and should be used in all glioma resected with functional location surgery [15].

The aim of the current research is to compare the electrical threshold needed for eliciting muscular response, and the proximity of the stimulated point to the pyramidal tract, in different regions of the temporal lobe. Specifically, in regions adjacent to the internal capsule and the cerebral peduncle.

1. **Research Goal and Hypothesis**

We will characterize the unique electrophysiological signature of the cerebral peduncle as opposed to the signature of internal capsule among patients with intraaxial temporal lobe tumors.

We hypothesize that the response from regions in proximity to the cerebral peduncle will be more condensed in comparison with a more scattered response from the regions adjacent to the internal capsule. To be more specific, we assume that in the same electrical power and distance of the eliciting point from the PT, the subcortical stimulation of the cerebral peduncle will evoke a wider muscular response of many more muscle groups compared to a more confined reaction of less muscle groups by internal capsule stimulus.

1. **Study Design**
* The study is a retrospective analysis of patients who underwent surgical resection of intraaxial tumors adjacent to motor pathways in the temporal lobe, using intraoperative electrophysiological mapping, in the neurosurgery department in Tel-Aviv Medical Center between 2016-2018.
* The study is based on reviewing patients' medical files, assessing the proximity of electrophysiological stimulus to the pyramidal tract, especially to the internal capsule and the cerebral peduncle.
* The study has been authorized by the Ethics Committee of the Tel-Aviv Medical Center for collecting retrospective data analysis (להוסיף מספר אישור כשיהיה).
1. **Methods**

**Research outline:** A retrospective cohort analysis, review of 25 ((בבדיקה patients’ files who underwent surgical resection of intra-temporal tumors adjacent to CSTs, using intraoperative electrophysiological mapping, in the neurosurgery department of Tel-Aviv Medical Center between 2016-2018.

**Study population:** Patients over 18 years old, who underwent surgical resection surgery in the temporal lobe in proximity to motor pathways, using intraoperative electrophysiological mapping, between 2016-2018.

**Exclusion Criteria:**

* Patients without electrophysiological, radiological and clinical follow up records.
* Patients under 18 years old.
* Patients who underwent surgical resection of intraaxial tumors before the relevant temporal lobe resection.
* Patients who have Space Occupying Lesion between the two temporal lobes that attaches to the pyramidal tract.

**Sample Size:** N = 25 patients לחשב את המספר המדויק))

**Variables:**

* Independent Variables:
1. Pre-operation Distance from pyramidal tract
2. Pre-operation Distance from internal capsule
3. Pre-operation Distance from cerebral peduncle
4. Tumor volume pre-operation
5. Tumor residual volume
6. Extent of resection
7. Age
8. Gender
9. Dominance
10. Co-morbidity
11. Pre-operative KPS
12. Tumor side and location
13. Pre-operative tumor volume
14. Presenting symptoms
15. Pre-operative muscle strength assessment
16. Surgery under general anesthesia / awake
17. Post-operative KPS
18. Post-operative muscle strength assessment
19. Post-operative complications
20. Histopathological type
* Dependent Variables:
1. Overall survival in months
2. DcMEP Threshold
3. Minimal ScrtMEP
4. Post-operative complications
5. Post-operative motor deficit
6. post-operation Distance from pyramidal tract
7. post-operation Distance from internal capsule
8. post-operation Distance from cerebral peduncle

**Research Conduct:**

* Collecting data from medical records of patients who underwent surgical resection of temporal tumors in proximity to the corticospinal tracts.
* Produce an Excel chart of the data with the relevant categories to the study.
* Define the distance of the tumor resections from the corticospinal tracts in different regions of the temporal lobe.
* Compare the motor response from regions in proximity to cerebral peduncle and the response from regions in proximity to internal capsule.
* Evaluate the neurological defects derived from damage to the above-mentioned regions and show the relation between the actual proximity to the CSTs and the motor response.

**Statistical Methodsלהשלים מה שמסמון באדום לא צריך לעבור הגהה**

All statistical analyses will be performed using the statistical software Statistical Package for Social Science (SPSS), version 20 (IBM SPSS Inc., Chicago, IL, USA). Descriptive statistics such as frequencies, percentages, means, ranges and standard deviations (SD) will be used to describe the data. Categorical data will be expressed as the absolute number and percentage, whereas continuous data will be expressed as the mean ± SD if normally distributed or as the median (interquartile range) if skewed. The Kolmogrov–Smirnov test or the Shapiro–Wilk test will be used to test the normality of continuous data. The Pearson chi-square test with continuity correction will be used to examine the association between categorical variables. When the expected cell count will be more than 20% or less than 5, the Fisher exact test was used. Cramer’s Vcorrelation test will be used to examine the correlation between two nominal groups, such as \_\_\_\_\_\_\_. The Pearson correlation will be used to examine the correlation between two continuous data groups, such as \_\_\_\_\_\_\_\_.

1. **Potential Biasלהשלים**
2. **Practical work by the student**

The student will:

* Overview and collect relevant clinical data from medical files of patients who underwent a temporal tumor resection.
* Summarize the data in an Excel chart.
* Perform volumetric and clinical analysis.
* Process the analysis with the neurophysiological data.
* Perform a statistical analysis.
* Describe the conclusions in the final paper.
1. **Study Significance**

 Patients who underwent surgical resection in proximity to Motor Pathways generally suffer from motor disabilities. Many techniques have been developed to improve the ability to resect tumors in a more precise and broad manner. Nowadays we acknowledge the potential of intraoperative neurophysiological stimulation monitoring. Much effort is invested in this field.

However, it has not been determined yet if we can differentiate between regions of the temporal lobe by getting different electrophysiological signals from every region. We believe that if we find our hypothesis to be right, this knowledge will help neurosurgeons and clinical neurophysiologists to perform more accurate monitoring during surgeries. As the accuracy of ISM will be better, we hope that neurosurgeons will be able to provide better outcomes for temporal tumor resection surgeries and fewer motor disabilities for the patients.

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