Department of Neurosurgery, University Hospital Münster
Department of Neurosurgery, University of Leiden
EANS-Young Neurosurgeons Research Collaboration

European multi-center trial on surgical outcome in juxta-medullary tumors

Study Protocol

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Version 1.0
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Eliminado: 27
1. Synopsis

Synopsis

Coordinating investigator

PD Dr. Michael Schwake, Klinik für Neurochirurgie, Universitätsklinikum Münster, Albert-Schweitzer-Campus 1, Geb. A1, 48149 Münster, Germany

Investigators

Michael Schwake, MD., Valerie ter Wengel, MD., Ehab Shiban, MD., Christian Ewelt, MD., Maria Louisa Gandia Gonzales, MD., PhD., Wilco Peul, MD, PhD, Jiri Bartek, MD, PhD., Martin Stienen, MD., Stephanie Schipmann, MD, PhD., Laura Lippa, MD, Toma Spiriev MD, Diogo Belo, MD., Evangelos Drosos, MD., Christina Aldea, MD., Nati Ben-Shalom, MD., Christian Freyschlag, MD, Stanislav Krapovoy, MD., Milan Lepic, MD., Katrin Rabiei, MD., PhD., Giovanni Raffa, MD., PhD., Cesare Zoia MD., Kathleen Seidel, MD., Mario Ganau, MD., PhD.

Title

multi-center trial on surgical outcome in juxta-medullary tumors

INDICATION

Adult patients operated on juxta-medullary tumors

Primary objectives:

Primary objectives are to assess the surgical outcome in the form of resection degree, functionality, and treatment patterns of juxta-medullary tumors in the modern-day era

Secondary objectives:

Assessment of variables leading to better outcome through regression analysis.
Assessment of treatment variations
Assessment of progression free survival
Assessment of overall survival

Inclusion/Exclusion criteria

Inclusion criteria

- Patients treated on intraspinal, extra medullary tumors
- Exclusion criteria
- Intraspinal metastasis
- Non-tumorous pathologies

Inclusion criteria

Eliminado: Adult, age ≥18 years, p
Eliminado: intradural
Eliminado: Patients must have sufficient cognitive and language skills to give informed consent
Con formato: Fuente: Sin Negrita

E Con formato: Párrafo de lista, Con viñetas + Nivel: 1 + Alineación: 0,63 cm + Sangría: 1,27 cm

Comentado [JB1]: So here is the first hurdle, if you go for informed consent, in the Nordics the ethics will take much more time, it is here I believe you should divide the study into a retrospective (informed consent waived) and prospective part... or how are the ethics in Germany, do you need informed consent even for retrospective datasets...

Eliminado: Lack of ability to consent

Con formato
• Intra-medullary tumors

Primary Outcome

• Extent of tumor resection
• Postoperative Neurological status (McCormick Score) (see CRF).

Secondary Outcome

Further patient reported outcome scores via:

Optional scales for neurological status: modifies JOA score (see CRF)
Optional assessment of functionality according the ODI and NDI scores (see CRF)
Length of hospital stay
30 days readmission
Infections
Blood loss
Duration of surgery
Progression of the disease or recurrence
Other complications (see CRF)

Mortality

Study design

multi-centric retrospective trial

Statistical analysis

Primary Outcome
Comparative analysis of pre-operative, post-operative and follow-up imaging, neurological status, according to the McCormick scale

Secondary Outcome

Con formado: Sangría: Izquierda: 1,27 cm. Sin viñetas ni numeración

Eliminado: <#>Quality of life based on the questionnaire (EDS) – prospective cohort

Comentado [JB2]: Even here, we should split in 2 parts (retro and prospective) otherwise there is a risk of confusion

Eliminar: <#>Functionality: Neck disability index (NDI) for tumors in the cervical spine, Oswestry disability index (ODI) for tumors in the thoracic and lumbar spine (see CRF) – prospective cohort

Pain (VAS) (see CFR) – prospective cohort

Neurological status (mJOA score)

Eliminado: AE should be classified according to the Landriel Ibanez classification for neurosurgical complications: grade I represents any non-life-threatening complication treated without invasive procedures; grade II is complications requiring invasive management; grade III is life-threatening adverse events requiring treatment in an intensive care unit (ICU); grade IV is death as a result of complications. We sought to compare our results with reports from the literature.

Eliminado: Here you should add resection and standardized complication outcome (i.e. the Ibanez scale)

Eliminado: Registry trial, both retrospective and prospective...

Eliminado: and questionnaires
Descriptive data analysis of clinical parameters is performed. Confidence intervals for relevant treatment effects are calculated using univariate and multi-variate statistical tests.

<table>
<thead>
<tr>
<th>Number of cases</th>
<th>Time period</th>
</tr>
</thead>
<tbody>
<tr>
<td>N= no limit, minimum 1000 patients</td>
<td></td>
</tr>
</tbody>
</table>

Patients treated between 2010 to 2022

<table>
<thead>
<tr>
<th>Number of centers</th>
<th>Study Centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>N= 24 (Planned)</td>
<td>In Germany (Planned):</td>
</tr>
</tbody>
</table>

1) Klinik für Neurochirurgie, Universitätsklinikum Münster (Michael Schwake)
2) Klinik für Neurochirurgie, Universitätsklinikum Augsburg (Ehab Schiban)
3) Klinik für Neurochirurgie, St. Barbara-Klinik Hamm-Heesen (Christian Ewelt)

In other European countries (Planned):

1) Department of Neurosurgery, University Neurosurgical Center Holland; LUMC [HMC] HAGA, Netherlands (Valerie ter Wengel)
2) Neurosurgery, University Hospital Bergen, Norway (Stephanie Schipmann)
3) Department of Neurosurgery, Hospital Universitario La Paz, Madrid, Spain (Maria L. Gandia Gonzalez)
4) Department of Neurosurgery, Azienda Ospedaliero Universitaria Senese LeScotte, Siena, Italy (Laura Lippa)
5) Department of Neurosurgery, Acibadem City Clinic Tokuda Hospital Sofia, Bulgaria (Toma Spiriev)
6) Department of Clinical Neuroscience, Karolinska Institutet and Department of Neurosurgery, Karolinska University Hospital, Stockholm, Sweden (Jiri Bartek Jr.)
7) Department of Neurosurgery, Rigshospitalet, Copenhagen, Denmark?
8) Neurosurgery Department, Centro Hospitalar Lisboa Norte (CHLN), Lisbon, Portugal (Diogo Belo)
9) Salfort Royal NHS Foundation Trust, Manchester, United Kingdom (Evangelos Drosos)
10) Department of Neurosurgery, Cluj County Emergency Hospital, University of Medicine and Pharmacy Iuliu Hatieganu, Cluj-Napoca, Romania (Christina Aldea)
| 11) Department of Neurosurgery, Rabin Medical Center, Belinson Campus, Petah Tikva, Israel (Nati Ben-Shalom) |
| 12) Department of Neurosurgery, Medical University of Innsbruck, Innsbruck, Austria (Christian Freyschlag) |
| 13) Burdenko Neurosurgical Center, Department of Spinal and Peripheral Nerve Surgery, Department of International Affairs, Moscow, Russia (Stanislav Kaprovoy) |
| 14) Clinic for Neurosurgery, Military Medical Academy, Belgrade, Serbia (Milan Lepic) |
| 15) Institution of Neuroscience & Physiology, Sahlgrenska Academy, Gothenberg, Sweden (Katrin Rabiei) |
| 16) Division of Neurosurgery, BIOMORF Department, University of Messina, Messina, Italy (Giovanni Raffa) |
| 17) Department of Neurosurgery and Spine Center of Eastern Switzerland, Cantonal Hospital St. Gallen, St. Gallen, Switzerland (Martin Stienen) |
| 18) Neurosurgery Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy (Cesare Zoia) |
| 19) Department of Neurosurgery, Inselspital Bern, Berne, Switzerland (Kathleen Seidel) |
| 20) Department of Neurosurgery, Oxford University Hospitals (Mario Ganau) |

Comentado [MS6]: Germany and other countries are divided here due to formal issues of the ethical committee. Which centers would do retrospective and which also prospective?
### 1.2 Flow chart

<table>
<thead>
<tr>
<th></th>
<th>Admission</th>
<th>Surgery</th>
<th>Discharge</th>
<th>Last Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessment of inclusion and exclusion criteria</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed consent/assent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological status: motor function, ataxia, reflexes</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>VAS Back pain, radiculopathy</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>McCormic score</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imaging (MRI)</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>EQ-5D*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mJOA/NDI/ODI*</td>
<td>X</td>
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<td></td>
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<tr>
<td>Approach</td>
<td>X</td>
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<tr>
<td>LOS</td>
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<td>X</td>
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<tr>
<td>Readmission</td>
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<td></td>
</tr>
<tr>
<td>Adjuvant treatment</td>
<td></td>
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<tr>
<td>Complications</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

* Optional
2. Introduction

2.1 Background information

Juxta-medullary tumors are mostly benign tumors in the spinal canal that may cause neurological deficits due to spinal cord or nerve root compression. The knowledge about the natural course of the disease, optimal treatment regarding timing of surgery and surgical approach are based on case series from different institutions around the world (Montano et al., 2016; M. Safaee et al., 2015, 2016; M. M. Safaee et al., 2017; Safavi-Abbasi et al., 2008; Schwake et al., 2018; Takahashi et al., 2022) (Montano et al., 2016; M. Safaee et al., 2015, 2016; M. M. Safaee et al., 2017; Safavi-Abbasi et al., 2008; Schwake et al., 2018; Takahashi et al., 2022) (Montano et al., 2016; M. Safaee et al., 2015, 2016; M. M. Safaee et al., 2017; Safavi-Abbasi et al., 2008; Schwake et al., 2018; Takahashi et al., 2022) (Montano et al., 2016; M. Safaee et al., 2015, 2016; M. M. Safaee et al., 2017; Safavi-Abbasi et al., 2008; Schwake et al., 2018; Takahashi et al., 2022) (Montano et al., 2016; M. Safaee et al., 2015, 2016; M. M. Safaee et al., 2017; Safavi-Abbasi et al., 2008; Schwake et al., 2018; Takahashi et al., 2022) (Montano et al., 2016; M. Safaee et al., 2015, 2016; M. M. Safaee et al., 2017; Safavi-Abbasi et al., 2008; Schwake et al., 2018; Takahashi et al., 2022) (Montano et al., 2016; M. Safaee et al., 2015, 2016; M. M. Safaee et al., 2017; Safavi-Abbasi et al., 2008; Schwake et al., 2018; Takahashi et al., 2022) (Montano et al., 2016; M. Safaee et al., 2015, 2016; M. M. Safaee et al., 2017; Safavi-Abbasi et al., 2008; Schwake et al., 2018; Takahashi et al., 2022) (Montano et al., 2016; M. Safaee et al., 2015, 2016; M. M. Safaee et al., 2017; Safavi-Abbasi et al., 2008; Schwake et al., 2018; Takahashi et al., 2022) (Montano et al., 2016; M. Safaee et al., 2015, 2016; M. M. Safaee et al., 2017; Safavi-Abbasi et al., 2008; Schwake et al., 2018; Takahashi et al., 2022) (Montano et al., 2016; M. Safaee et al., 2015, 2016; M. M. Safaee et al., 2017; Safavi-Abbasi et al., 2008; Schwake et al., 2018; Takahashi et al., 2022) (Montano et al., 2016; M. Safaee et al., 2015, 2016; M. M. Safaee et al., 2017; Safavi-Abbasi et al., 2008; Schwake et al., 2018; Takahashi et al., 2022) (Montano et al., 2016; M. Safaee et al., 2015, 2016; M. M. Safaee et al., 2017; Safavi-Abbasi et al., 2008; Schwake et al., 2018; Takahashi et al., 2022). Moreover, little is known about the long-term clinical and functional outcome after tumor resection, indicators of quality of treatment and quality of life after surgery.

Main treatment option of juxta-medullary tumors is a neurosurgical resection. The main goal of the surgery is to decompress the neuro structures in order to reveal neurological deficits. However, achieving gross total resection (GTR) is important in order to achieve long progression free survival (PFS) (Lenzi et al., 2017; Nanda et al., 2015; Ottenhausen et al., 2019; Ozawa et al., 2007) (Lenzi et al., 2017; Nanda et al., 2015; Ottenhausen et al., 2019; Ozawa et al., 2007) (Lenzi et al., 2017; Nanda et al., 2015; Ottenhausen et al., 2019; Ozawa et al., 2007) (Lenzi et al., 2017; Nanda et al., 2015; Ottenhausen et al., 2019; Ozawa et al., 2007) (Lenzi et al., 2017; Nanda et al., 2015; Ottenhausen et al., 2019; Ozawa et al., 2007) (Lenzi et al., 2017; Nanda et al., 2015; Ottenhausen et al., 2019; Ozawa et al., 2007) (Lenzi et al., 2017; Nanda et al., 2015; Ottenhausen et al., 2019; Ozawa et al., 2007). Therefore, the surgeon should choose the appropriate surgical approach to achieve these goals. On the other hand, to large exposure may lead to impaired recovery after surgery, eventual higher blood loss during surgery and thus longer stay in hospital (LOS) and impaired quality of life. Moreover, extensive bone resection may lead to spinal instability requiring instrumentation, during index surgery or during further follow up (Abumi et al., 1990; Jiang et al., 2022; Lee & Teo, 2004; Mummaneni et al., 2020; Raysi Dehordi et al., 2012) (Abumi et al., 1990; Jiang et al., 2022; Lee & Teo, 2004; Mummaneni et al., 2020; Raysi Dehordi et al., 2012) (Abumi et al., 1990; Jiang et al., 2022; Lee & Teo, 2004; Mummaneni et al., 2020; Raysi Dehordi et al., 2012) (Abumi et al., 1990; Jiang et al., 2022; Lee & Teo, 2004; Mummaneni et al., 2020; Raysi Dehordi et al., 2012) (Abumi et al., 1990; Jiang et al., 2022; Lee & Teo, 2004; Mummaneni et al., 2020; Raysi Dehordi et al., 2012) (Abumi et al., 1990; Jiang et al., 2022; Lee & Teo, 2004; Mummaneni et al., 2020; Raysi Dehordi et al., 2012).

Other concerns are safety requirements in order to prevent peri-operative complications. For example, the role of intra-operative neurophysiological monitoring. Some authors recommend the utilization...
intra operative monitoring, however, the evidence level is very low (Jesse et al., 2022; Thakur et al., 2021). Other open questions are for example methods for dura closure and thrombosis prevention.

On the other hand, some tumors can be treated with irradiation, some studies showed efficacy of this method mainly in the case of Schwannomas and meningoimias. In case of residual tumor or tumor progression irradiation can be also performed to prevent further growth (Chang & Lee, 2013). In case of residual tumor or tumor progression irradiation can be also performed to prevent further growth (Chang & Lee, 2013).

Lastly, in comparison to the methods mentioned above, a wait-and-see approach can be used for asymptomatic patients or those with mild symptoms. In this case, clinical and imaging examinations are performed at regular intervals to check the neurological status and the tumor. This can also be done for longer periods of time because of the benign nature of these tumors with the slow growth. In case of new neurological deficits of or progression surgical treatment should be advocated. Overall, it is not certain at what point therapy is indicated, especially in asymptomatic patients. As many these tumors are discovered by coincidence during imaging, which was performed due to other symptoms.

2.2 Rationale of the study

The rationale of the trial is to find out the optimal timing, method, and approach to treat juxta-medullary tumors. Because of the low incidence of juxta-medullary tumors, a multi-center trial seems to be essential. This would allow us to analyze a large number of patients, much more than any other published paper. Moreover, the different protocols and standards approaches in each center would allow a conducting Comparative Effectiveness Research (CER).

2.3 Aims

The goal of this study is to establish a multicenter cohort of patients operated on a juxta-medullary tumors. With especial emphasis on functional outcome, quality of treatment and quality of life after surgery three months after surgery. Causes of unfavorable outcome should be determined (Schipmann et al., 2017, 2019).

Hypothesis is that early and less-invasive surgery with maximal extents of resection would lead to more favorable outcome and longer PFS. Primary Outcome are determined by:

- Quality of life based on the questionnaire (EDS)
- Extent of tumor resection
- Neurological status (McCormick Score).

Secondary outcomes are the role of intraoperative monitoring, dura closure techniques and role of microsurgery and should be determined using further patient reported outcome scores:

- Functionality: NDI for tumors in the cervical spine, ODI for tumors in the thoracic and lumbar spine
- Pain (VAS), neurological status (mJOA score), in addition to length of hospital stay, 30 days readmission, infections, blood loss, duration of surgery, progression of the disease or recurrence, other
complications and mortality

2.3 Methodology
All patients treated in one of the study centers are recorded in a databank (Redcap, see below), which includes information about admission, surgery and neurological outcome would be evaluated. The neurological status according to the McCormick scale and other information would be assessed according to the hospital records (see CRF). If additional data is known or documented in hospital records it can be added too, for example questionnaires on quality of life and functionality. Additional data can be obtained by contacting patients again.

Univariate and multivariate statistics would be applied to prove which variables might lead to a favorable or unfavorable outcome.

A minimal number of about 1000 patients is expected to be sufficient for conclusions regarding the preliminary outcomes.

2.4 Risk-Benefit Analysis

2.4.1 Risk expected for participants
No risk whatsoever awaits the participants in the study. All examinations and interventions will be performed according to clinical routine. Refusal to participate in the study will not result in any disadvantages for the patients. Participants will be treated exactly like non-study participants, based on the therapy standards of the respective study center.

2.4.2 Benefit expected for participants
There is no specific benefit for the participants by taking part in the study.

2.4.3 Benefit expected for medical science
The study should determine factors that influence the outcome (degree of resection, neurology, quality of life functionality, pain) of the patients. Furthermore, it would determine factors that influence the quality of treatment (length of stay, 30-day readmission, complications, infections etc.).

2.4.4 Benefit expected for the society:
A postoperatively impaired quality of life, severe neurological deficit, or functionality often leads to high costs in the health and social care systems. Therefore, knowledge of influencing factors is also of imminent societal importance.

In addition, quality indicators of therapy should be determined. These are also important for society. Improving the quality of therapy, for example, by reducing the length of stay, postoperative complications can also reduce treatment costs.
3. Objectives and Endpoints

3.1 Objectives

3.1.1 Primary Objective

Primary objectives are to assess the functionality, quality of life and quality of treatment of patients treated on juxta-medullary tumors, in addition the extent of resection of the tumor will be assessed.

3.1.2 Secondary Objectives

Assessment factors leading to better outcome, potential complications, progression free survival, and overall survival

3.2 Endpoint

3.2.1 Primary endpoint

The extent of resection will be evaluated using on post-operative imaging. And the neurological status using the McCormick Scale (see CRF).

3.2.2 Secondary endpoints

Secondary outcomes are:
- Length of hospital stay, 30 days readmission, Infections, Blood loss, Duration of surgery, Progression of the disease or recurrence, other complications (see CRF), Mortality

4. Study Design

5. Study Sites and Study Population

5.1 Study Site Selection

Due to the rare nature of juxta-medullary tumors and in order to have the opportunity to compare different treatment methods, the trial is planned as a multi-center trial. So far, 24 centers have expressed interest in participating in the study. Most of them as part of the EANS-Young Neurosurgeons Research Collaboration Initiative.

1) Klinik für Neurochirurgie, Universitätsklinikum Münster, Germany
2) Klinik für Neurochirurgie, Universitätsklinikum Augsburg, Germany
3) Klinik für Neurochirurgie, St. Barbara-Klinik Hamm-Heesen, Germany
4) Department of Neurosurgery, University Neurosurgical Center Holland; LUMC|HMC|HAGA, Netherlands
5) Neurosurgery, University Hospital Bergen, Norway
6) Department of Neurosurgery, Hospital Universitario La Paz, Madrid, Spain
7) Department of Neurosurgery, Azienda Ospedaliero Universitaria Senese LeScotte, Siena, Italy
8) Department of Neurosurgery, Acibadem City Clinic Tokuda Hospital Sofia, Bulgaria
9) Department of Clinical Neuroscience, Karolinska Institutet and Department of Neurosurgery, Karolinska University Hospital, Stockholm, Sweden
5.2 Study Population

5.2.1 Inclusion Criteria

- Patients treated on intraspinal, extra medullary tumors

5.2.2 Exclusion Criteria

- Intraspinal metastasis
- Non-tumorous pathologies
- Intra-medullary tumors

5.2.3 Distribution of Gender in the Study Population

All patients treated on juxta-medullary tumors can be invited to participate in the study; distribution of Gender varies depending on histology. For example, spinal meningiomas are up to 80% in female patients. [Schwake et al., 2018] [Schwake et al., 2018] [Schwake et al., 2018] [Schwake et al., 2018] [Schwake et al., 2018] [Schwake et al., 2018] [Schwake et al., 2018] [Schwake et al., 2018].

6. Patient Registration
Patients who are cared for at one of the study sites and who are possibly eligible will be invited for study participation. Once written informed consent in participation has been given, the center can assign a patient identification number consisting of a unique center code, a hyphen and a two digit continuously increasing number and register the patient in the trial-specific EDC system.

Should inclusion criteria be failed, or exclusion criteria arise during the following screening process, the patient must be reported to the study coordinator immediately and the patient will be withdrawn from the study.

7. Assessment of Safety
Patients are treated according to the protocol of each center, the participation in the trial does not cause any disadvantage for these patients.

8. Statistics
8.1 Primary outcome
Comparative analysis of pre-operative, post-operative, and follow-up imaging, neurological status.

8.2 Secondary outcome
Descriptive data analysis of clinical parameters will be performed. Confidence intervals for relevant treatment effects are calculated using univariate and multi-variate statistical tests.

Patients’ data will be compared to historical cohorts and equivalence, or superiority of care will be described.

9. Documentation, Data Management, Archiving
9.1 Patient Identification List
All patient data will be collected in a pseudonymized form. Every study patient can be identified by a unique patient identification number consisting of a country code (for example DE for Germany), a unique center code, a hyphen and three digit numbers. A confidential patient identification list which links the patients’ names with the patient identification number will be stored in the investigator site file.

9.2 Source Data / Source documents
Source data are, within the meaning of the ICH E6 Guideline, all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data will be documented in various source documents (e.g. hospital records, doctor’s report, patient’ diaries or evaluation checklists, x-rays) and then entered into the electronic Case Report Form (eCRF).
9.3 Recording of Data / Case Report Form (CRF)

Data will be recorded electronically using an EDC (Electronic Data Capture) system. For the documentation of study data, the investigator will be given access to an electronic CRF (eCRF) for each recruited patient. Only persons authorized to enter data into the eCRF will have access to the EDC system. All users will be trained to use the EDC system and will comply with the instructions in the study-specific user manual. They will have continuous access to the data and reports of study patients at their own study site. The investigator is responsible for ensuring that the study data will be documented correctly, completely and in a timely manner. A study team physician takes on responsibility for the collected data by signing electronically.

9.4 Data Management

For data management, the validated data management system redcap will be used. All entered data will be stored on servers of the University of Münster (WWU). The servers are located in a secure data center and behind a firewall in the network of the University of Münster (WWU). A backup of the data will be saved on a daily basis and all data changes will be recorded in an audit trail.

All data will be checked for plausibility during initial data entry. Missing or non-plausible data are highlighted by the system right at input at the clinical study site and may be corrected immediately. Thereafter, according to the data validation plan, further data checks will be performed with regard to completeness and plausibility by the study coordinator. In case of non-plausible or missing data, queries will be sent to the study site.

9.5 Archiving

After the end of the trial the originals of all trial specific documents (Trial Master File) including originals of the CRFs will be stored by the sponsor for at least 10 years in accordance with the applicable regulations (GCP-Verordnung §13(10)), EU directive 536/2914 and applicable EU directives on medical devices).

Furthermore, the investigator stores the ISF (Investigator Site File) including copies of the CRFs for the time period given above.

No trial data or documents must be destroyed without prior written agreement between the study coordinator and the investigators or their designee. queries must be resolved by authorized members of the investigator’s staff in the respective study site in a timely manner.

After completion of data entry and data processing, the database will be locked and the data will be exported for statistical analysis. The investigator will receive a CD-ROM of the eCRF data for archiving at the clinical study site.

10. Monitoring, Audits and Inspections

13.1 Monitoring
A quality assurance audit may be conducted by the study coordinator or one of his designees. The quality assurance auditor must be provided access to all medical records, the investigator’s study-related files and correspondence, and the informed consent documentation that is relevant to this study.

11. Ethical and Regulatory Requirements

11.1 Declaration of Helsinki and Legal Requirements

The study will be conducted in compliance with the declaration of Helsinki (current version, October 2013, Fortaleza), the current legal provisions regarding data protection, and the principals of Good Clinical Practice.

The present study will not be started in a country before the competent ethics committee has given a favorable opinion and an approval by the relevant competent federal authority has been obtained. Besides, for each participating study site a favorable opinion of the respective ethics committee is required.

In case of substantial amendments, a new application will be submitted to the ethics committees and/or the competent federal authorities. Changes will not be implemented in a country unless the competent ethics committee has given a favorable opinion and/or the competent authority has granted an approval.

Issues, which always require a favorable opinion of the ethics committee, are for example:

1. Inclusion of additional study sites,
2. Change of the investigator or his deputy,
3. Changes in any documents addressed to study participants or in any study information addressed to potential study participants.

11.2 Patient Information and Informed Consent

12.3 Financing

External funding is currently not planned. If funding is requested and approved during the course of the study, the Ethics Committee must be notified immediately.

12.4 Adherence to the Protocol

The investigator must adhere to the protocol as detailed in this document. Dependent on competence, substantial changes to the protocol will require written favorable opinion by the ethics committee and/or written approval by the competent authority prior to implementation. This does not apply for appropriate urgent safety measures taken to protect the subjects against any immediate hazard.

Any deviations from the protocol must be fully documented in the source documentation and recorded and explained in the CRF.

13 Study Registration, Reporting and Publication
13.1 Study registration

The study is registered in a clinical trials database, which is accessible to the public (www.clinicaltrials.gov; NCT04738162).

13.2 Publication Policy

After complete data collection and analysis, the study results will be published. Single publications such as lectures, posters or papers principally require the approval of the Principal Investigator. Inquiries by the press or the public regarding study results are only to be answered by the Principal Investigator.

A manuscript is to be prepared by the Principal Investigator or by a designated co-worker after receiving the biometric report. All contributors would be considered as co-authors. The co-authors are required either to agree to the manuscript or to indicate any requests for changes within 4 weeks after receiving the draft of the manuscript to the lead author. Should they fail to meet this requirement agreement will be assumed.

14. Supplements:

14.1 McCormick scale

1. Neurologically intact, ambulates normally, may have minimal dysesthesia
2. Mild motor or sensory deficit; patient maintains functional independence
3. Moderate deficit, limitation of function, independent with external aid
4. Severe motor or sensory deficit, limit of function with a dependent patient
5. Paraplegic or quadriplegic, even if there is flickering movement

14.2 Classification of postoperative complications according Landriel Ibanez classification for neurosurgical complications: [Ibanez et al., 2011]

1. Grade I represents any non-life threatening complication treated without invasive procedures
2. Grade II is complications requiring invasive management
3. Grade III is life-threatening adverse events requiring treatment in an intensive care unit (ICU)
4. Grade IV is death as a result of complications. We sought to compare our results with reports from the literature.
15. References:


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