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Evaluation of patient STress level caused by radiological Investigations in early Postoperative phase After CRANIOTomy (IPAST-CRANIO): protocol of a Swiss prospective cohort study

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Manuscripts

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4 **Evaluation of patient STress level caused by radiological Investigations in early**
5 **Postoperative phase After CRANIOTomy (IPAST-CRANIO): protocol of a Swiss**
6 **prospective cohort study**
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Abstract

Introduction:

Postoperative imaging after neurosurgical interventions is usually performed in the first 72 hours after surgery to provide an accurate assessment of postoperative resection status. Patient frequently report that early postoperative examination after craniotomy for tumor and vascular procedures is associated with distress, exertion, nausea, and pain. Delayed postoperative imaging (between 36 and 72 hours postoperatively) may have an advantage regarding psychological and physical stress compared to early imaging. The goal of this study is to evaluate and determine the optimal time frame for postoperative imaging with MRI and CT in terms of medical and neuroradiological implications and patient's subjective stress level.

Methods and Analysis

Data will be prospectively collected from all patients aged 18 to 80 years who receive postoperative MRI or CT imaging following a craniotomy for resection of a cerebral tumor (benign and malignant) or vascular surgery. Participants have to complete questionnaires containing visual analogue scores for headache and nausea (VAS), Body Part Discomfort score and a single question addressing subjective preference of timing of postoperative imaging after craniotomy. The primary endpoint of the study is the difference in subjective stress due to imaging studies after craniotomy, measured just before and after postoperative MRI or CT with the above mentioned instruments. Subjective stress is defined as a combination of the scores VAS pain, VAS nausea, and $0.5 \times$ Body Part Discomfort score.

This study determines whether proper timing of postoperative imaging can improve patient satisfaction and reduce pain, stress and discomfort caused by postoperative imaging. Factors causing additional postoperative stress are likely responsible for delayed recovery of neurosurgical patients.

Ethics and Dissemination

The institutional review board (Kantonale Ethikkommission Zürich) approved this study on 4 August 2020 under case number BASEC 2020-01590. This trial has also been registered in Clinical Trials under ClinicalTrials.gov ID: NCT05112575.

Keywords

Magnetic resonance imaging – computed tomography - craniotomy – postoperative imaging

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers.

The order of the items has been modified to group similar items (see <http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/>)

| | |
|---|--|
| Title {1} | Evaluation of patient stress level caused by radiological investigations in early postoperative phase after craniotomy (IPAST-CRANIO) |
| Trial registration {2a and 2b} | <p>The institutional review board (Kantonale Ethikkommission Zürich) approved this study on 4 August 2020 under case number: BASEC 2020-01590.</p> <p>This trial has also been registered in Clinical Trials under ClinicalTrials.gov ID: NCT05112575.</p> |
| Protocol version {3} | 1.0, 25.06.2020 |
| Funding {4} | This research is financed by the Department of Neurosurgery, University Hospital Zurich, Switzerland. |
| Author details {5a} | <p>Lazar Tosic, MD</p> <p>Marco Thoma, cand. MScN</p> <p>Stefanos Voglis, MD</p> <p>Anna-Sophie Hofer, MD, PhD</p> <p>A. Pangalu, MD</p> <p>Luca Regli, MD</p> <p>Menno R. Germans, MD, PhD</p> |
| Name and contact information for the trial sponsor {5b} | <p>Prof. Dr. Luca Regli</p> <p>E-Mail: luca.regli@usz.ch</p> |

| | |
|----------------------|--|
| | Tel.: +4144255992 |
| Role of sponsor {5c} | Design; management, analysis and interpretation of data; critically reviewing the manuscript; and the decision to submit the report for publication. |

Background and rationale {6a}

Magnetic resonance imaging (MRI) after neurosurgical resection of a cerebral tumor is usually performed in the first 72 hours after surgery. (1-4) accurate assessment of early postoperative resection status of brain tumors is mandatory for further treatment planning, e.g., delineation of the radiation field during radiotherapy, or reoperation for significant residual tumor. (5) Various MRI-sequences provide information on tumor size and location, as well as additional insight into secondary phenomena such as edema, hemorrhage, infarct, necrosis, and signs of increased intracranial pressure. (1, 3, 5, 6) The 72 hours time window is crucial for accurate assessment of resection status and is additionally used for quality control of neurosurgical procedures. (7) Postoperative MRI performed later than 72 hours after surgery can lead to false positive contrast enhancement due to absorption of contrast in the surgical area which can complicate the assessment of resection status. (1, 6) Postsurgical repair mechanisms at the resection site resulting from hypervascularization and disruption of the blood-brain barrier are probably responsible for this delayed enhancement. (7)

The potential advantages of early imaging (within 36 hours after surgery) are better radiological assessment of the surgical site and earlier diagnosis of postoperative complications, such as infarcts, postoperative bleeding or edema. This may help improve the postoperative management of patients with complications. Moreover, earlier information about the outcome of surgery could also lead to psychological relief for patients in the early postoperative period. Disadvantages of early postoperative examinations after craniotomy are frequently reported by patients and include distress, exertion, nausea, and pain during and after the examination. As such, psychological and physical patient stress could be a potential disadvantage of early (within 36 hours after surgery) MRI examination. An alternative image modality is computed tomography (CT), which may be less stressful for patients as it takes only 5 to 10 minutes to complete the scan and patients do not have to lie in a narrow scanner as for MRI examinations. However, with this modality the postoperative resection status cannot be reliably assessed. To our knowledge, no previous literature has been published which addressed stress factors during postoperative imaging. To our opinion, a more patient-centered design of the early postoperative course including timing of postoperative imaging studies requires the investigation of patient stress levels associated with postoperative imaging performed at different time intervals from surgery. With the optimization of the postoperative time window for MRI and CT examinations we aim to improve psychological

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3 and physical patient stress, which may have a positive influence on early recovery.
4 Additionally, establishing an optimal time window for postoperative MRI imaging will help
5 in scheduling the examination before the elective surgical treatment. This will have a positive
6 impact on preparing patients, radiology employees, nurses and physicians for a smooth and
7 easy transport to and from the MRI examination.
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10 11 12 **Objectives {6a}**

13 The goal of this study is to assess whether early imaging with MRI (within 36 hours) after
14 craniotomy has a different impact on patient stress compared to delayed imaging (between 36
15 and 72 hours). Secondly, we aim to assess whether there is a difference in patient stress level
16 between postoperative MRI and CT performed within 72 hours postoperatively.
17

18 The authors hypothesize that delayed MRI imaging after craniotomy is more comfortable for
19 patients without having negative implications on the validity and reliability of radiological
20 assessments compared to imaging performed within 36 hours. Secondly, we hypothesize that
21 postoperative MRI is more stressful for patients than postoperative CT.
22
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26 27 **Trial design {8}**

28 The IPAST-CRANIO study (Evaluation of patient STress level caused by radiological
29 Investigations in early Postoperative phase After CRANIOtomy) is a patient-oriented,
30 prospective, exploratory cohort study.
31
32

33 **Methods: Participants, interventions and outcomes**

34 **Study setting {9}**

35 Data will be collected from patients between 18 and 80 years old who receive MRI or CT
36 follow-up studies after craniotomy for resection of a space occupying lesion (benign or
37 malignant) or vascular procedure at the Department of Neurosurgery at the University
38 Hospital Zurich.
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42 **Eligibility criteria {10}**

43 Participants fulfilling all of the following inclusion criteria are eligible for the study:
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45

- 46 • Written consent of the patient
- 47 • Age between 18 and 80 years
- 48 • Planned supra- or infratentorial (partial) resection of space occupying lesion (benign or
49 malignant) or vascular neurosurgical procedure (clipping of an aneurysm, resection of an
50 arteriovenous malformation/fistula, resection of cavernoma)
- 51 • Planned MRI or CT follow-up within 72 hours after surgery

52 The presence of any of the following exclusion criteria will lead to exclusion of the
53 participant:
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- No informed consent
- Surgery involving only one burr hole (e.g. biopsy) instead of craniotomy
- Not able to fill out the questionnaires due to cognitive impairment or aphasia
- Not German or English speaking
- Contraindication for MRI/CT examination
- No postoperative MRI or CT examination planned within 72 hours after surgery

Patient and Public Involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Who will take informed consent? {26a}

Patients will be informed verbally and in writing about the study by members of the study team. The information will be given at least one day before the surgical procedure to ensure enough time to consider participation. We emphasize that participation in the study does not impose a significant additional burden on patients as only short questionnaires need to be completed which do not entail any significant risks or unreasonable questions.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Furthermore, patients will be informed and educated in detail about other aspects:

- The intended further use of the non-genetic data for research purposes;
- Their right to refuse or withdraw consent at any time without justification;
- Their right to be informed of the results affecting their health and their right to waive this information;
- The measures taken to protect personal data;
- The possibility of sharing the personal data with third parties for research purposes.
- The collection of patients' consent will take place after the study has been approved by the Ethics Committee.

Interventions

Explanation for the choice of comparators {6b}

The authors hypothesize that the optimal period for postoperative imaging is 36 to 72 hours and therefore decided to include the early time frame (within 36 hours) as an adequate comparator. The authors will also compare the outcomes between the group undergoing postoperative CT and the group undergoing postoperative MRI.

Intervention description {11a}

In general, all patients in our institution receive postoperative imaging within the first 72 hours after a craniotomy for a space-occupying lesion or vascular procedure. The study

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3 intervention includes the completion of a questionnaire right before and after the
4 postoperative radiological investigation (Figure 1, see supplementary data). Patients are
5 divided in two groups depending on the time interval between end of surgery and radiological
6 investigation: late group (completing the questionnaire 36 to 72 hours after surgery) and early
7 group (completing the questionnaire within 36 hours after surgery). The time intervals to the
8 radiological investigation are assigned by coincidence and the patients are not randomized
9 into any group. The exact time interval until examination depends on various factors, e.g.:
10 capacity of the department of neuroradiology or weekday of surgery (patients operated on
11 Friday are more likely to receive postoperative imaging on Monday; patients operated on
12 Thursday are most likely receive it on Friday) and patient condition (early imaging will more
13 likely be performed in suspected postoperative complications). We decided to use this way of
14 defining the comparators as we a primariliy interested in examining potential differences
15 between groups, rather than assessing causality between delayed imaging and stress level.
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21 The questionnaire consists of visual analog scale (VAS) for headache, visual analog scale
22 (VAS) for nausea, and Body Part Discomfort Scale (Figures 2, 3 and 4). At the end of the
23 questionnaire, patients will be asked to answer the following question:
24

25 In your opinion, should the MRI and/or CT scan have been performed earlier or later? The
26 possible answers are:
27

- 28
29 Yes, earlier;
30 Yes, later;
31 No, I am satisfied with the timing of the exam.
32

33 The authors have chosen these scales because they are validated and simple to understand and
34 register. The completion of each questionnaire will take 5 to 10 minutes, and the burden for
35 each patient is assumed to be low as the questionnaires do not contain any unreasonable
36 questions.
37
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40 **Criteria for discontinuing or modifying allocated interventions {11b}**

41 Although patients might have signed the informed consent situations that do not allow for
42 completion of the questionnaires can occur. Reasons include postoperative complications
43 leading to imaging in intubated patients, emergency imaging in extubated patients, , or the
44 neurosurgeon's decision not to perform postoperative imaging due to case-specific
45 considerations. These patients will be excluded from analysis and the reason for not
46 completing the questionnaire will be registered.
47
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50 **Strategies to improve adherence to interventions {11c}**

51 This study is implemented in close and intensive collaboration with nursing staff and
52 supported by residents, medical students and administrative staff. Through this collaboration
53 the study team has managed to create sufficient resources ensuring a high and optimal
54 adherence to the intervention.
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59 **Relevant concomitant care permitted or prohibited during the trial {11d}**

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3 None, the interval to radiological investigation will not be delayed due to completion of the
4 questionnaire.
5

6 **Provisions for post-trial care {30}**

7 Participants will be informed about the results by an information letter, if interested. The
8 scheduling of future postoperative imaging will be planned based on this study's results.
9
10

11 **Outcomes {12}**

12 The primary endpoint of the study is the difference in subjective stress after craniotomy
13 measured right before and after postoperative MRI or CT imaging with the mentioned
14 instruments. Subjective stress is evaluated as a combination of the scores VAS pain, VAS
15 nausea, and 0.5* Body Part Discomfort score (Figures 2, 3 and 4). A minimum score of 4.5
16 and a maximum score of 42.5 can be achieved.
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20 The secondary endpoints of the study are divided into two groups:
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22 1. Patient specific secondary endpoint:

- 23 • patient interpretation of whether MRI follow-up was performed at the correct interval.
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28 2. Radiology specific secondary endpoints:

- 29 • residual tumor on MRI.
- 30 • contrast enhancement on MRI (postoperative reactive change, not tumor specific).
- 31 • significant post-operative bleeding.
- 32 • Infarction.
- 33 • residual perfusion of the aneurysm or AVM/AVF remnant.
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40 **Participant timeline (Figure 1) {13}**

41 Patients are screened on the hospital admission day by the study team and informed consent
42 is taken if inclusion criteria are fulfilled and if no exclusion criteria are met. Questionnaires
43 are completed by patients immediately before and after postoperative MRI or CT imaging.
44 The study is finished for each patient after having completed the post-investigational
45 questionnaire. If either or both questionnaire(s) cannot be completed, the patient's study
46 participating is finished after the radiological investigation. Radiological findings are
47 assessed and documented in writing by a neuroradiologist according to local guidelines.
48
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52 **Sample size {14}**

53 A sample measurement of VAS scores in 100 patients with craniotomy for tumour resection
54 in 2019 resulted in a mean score of 1.8 (VAS pain) and 0.8 (VAS nausea). Because there was
55 no baseline data for the Body Part Discomfort score, it was equated to the percentage of VAS
56 pain per patient. This resulted in an average Body Part Discomfort score of 12.3 points. For
57 calculating the total score, the VAS-scores and half of the points from the Body Part
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3 Discomfort score are used. The total mean score of all three measurements then becomes 13.6
4 (standard deviation 5.4). To measure an expected change of one third for the separate scores
5 with a power of 80% and a type I error of 5%, a total of 224 patients are required for the
6 study. To correct for any loss to follow-up, we will include 230 patients in this study.
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10 **Recruitment {15}**

11 The study team screens all the patients on the admission day based on demographics,
12 diagnosis and planned operation. All adult patients receiving craniotomy for a space
13 occupying lesion or vascular indications are asked to participate in the study.
14
15
16

17 **Data collection and management**

18 **Plans for assessment and collection of outcomes {18a}**

19 Data will be collected from all patients aged 18 to 80 years who receive postoperative MRI or
20 CT follow-up after craniotomy for resection of a cerebral space-occupying lesion (benign and
21 malignant) or vascular procedure using a questionnaire. Radiological findings are assessed
22 and documented in writing by a neuroradiologist according to local guidelines.
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28 The CRF collects the following information and scores:

- 29
30 - Demographic data of patients (sex, age)
31
32 - Localization of craniotomy (side, supra- or infratentorial, lobe and region)
33
34 - Time interval (in hours and postoperative day) between end of surgery and start of MRI or
35 CT scan
36
37 - Neuroradiology reports of postoperative imaging examinations
38
39 - Patient related criteria:
40
41
 - 42 • Visual analog scale (VAS) for headache (Figure 2).(8)
 - 43 • VAS for nausea (Figure 3).(8)
 - 44 • Body Part Discomfort Scale (Figure 4)(9).

45
46

47 At the end of the second questionnaire, patients will be asked to answer the following
48 question:
49

- 50 - In your opinion, should the MRI and/or CT scan have been performed earlier or later? The
51 possible answers are:
52
 - 53 ○ Yes, earlier;
 - 54 ○ Yes, later;
 - 55 ○ No, I am satisfied with the timing of the exam.

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60 The radiological criteria that will be examined are as follows:

- Location of tumor (supra- or infratentorial, left or right)
- Tumor remnant on MRI
- Contrast enhancement on MRI (postoperative reactive change, not tumor-specific)
- Significant postoperative hemorrhage
- Postoperative infarction
- Residual perfusion of the aneurysm or AVM/AVF remnant

Plans to promote participant retention and complete follow-up {18b}

In this study, patients will complete a questionnaire before and after postoperative radiological examination. At the morning rounds, nursing staff is informed about patients who are planned for radiological examination and who are included in the study. When the nursing staff is informed about the exact time for the MRI or CT, the attending nurse (supported by a resident or a medical student if necessary) gives the questionnaire to the patient. The nurse is continuously reminded for this step, thanks to a comment in the digital patient report system (KISIM). Nursing staff and medical staff will monitor the completion of the questionnaires and can support at any time.

Data management {19}

Source data are available as paper questionnaires from patients and as digital documentation in the hospital-wide patient report system (KISIM) for clinical and radiological information. These data are pseudonymized, coded and stored in the form of the coded data in two Microsoft Access tables. One table contains the patient's hospital identification number, date of birth, and study number. The second Microsoft Access table contains all coded study data and patients are identified by study number only. Both tables are protected with passwords and are stored in a secured folder and are only accessible for study team members. Completed questionnaires are stored in a closed cabinet (available in research office and only accessible to the Project Leader of the study).

Confidentiality {27}

Personal and medical data will be collected for this study. When data is collected for study purposes, the data is pseudonymized and coded. The coding ensures that all reference data that would reveal the identity of a patient (name, date of birth) is deleted and replaced by a key. The list of keys always remains in the institution/hospital. In the case of a publication, the summarized data cannot be traced back to an individual person. The name of a patient will never appear on the internet or in any publication.

17. Data storage details

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3 The generation, transfer, storage, and analysis of health data within the scope of this project is
4 carried out in strict compliance with the current legal provisions for data in Swiss Protection
5 and is carried out according to the HRO regulation Art. 5.
6

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8 All persons who have access to patient data within the scope of the study are subject to the
9 obligation of confidentiality.
10

11 It is possible that the study will be reviewed by the ethics committee or by the institution that
12 initiated the study. The investigator may have to disclose personal and medical data for such
13 controls. All persons must maintain absolute confidentiality.
14
15
16

17 **Statistical methods**

18 **Statistical methods for primary and secondary outcomes {20a}**

19 For data analysis, patients are being divided into 2 groups based on predefined time intervals:
20
21

- 22 1. early imaging: within 36 hours postoperatively.
- 23 2. late imaging: between 36 and 72 hours postoperatively.
- 24
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29 A second analysis is performed, dividing patients into the following groups:

- 30 1. early imaging: on the same day of surgery (day 0) or 1st postoperative day.
- 31 2. late imaging: on the 2nd or 3rd postoperative day.
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37 A third analysis will be performed, dividing the patients based on the radiological
38 examination performed (MRI or CT).
39

40 Descriptive data will be investigated for a normal distribution. In case of a normal
41 distribution, results will be presented as means with standard deviations and groups compared
42 by Chi-square tests. If not, the results will be presented as medians with interquartile ranges
43 and results of a non-parametric (Fisher's exact test) will be reported. Results of pre- and post-
44 imaging questionnaires are compared with the paired t-test, or Wilcoxon signed rank test in
45 case of a non-normal distribution of data. The primary outcome is assessed by subtracting the
46 mean subjective stress score before the investigation from the score after the investigation.
47 Crude and adjusted stress score differences are calculated in relation to the predefined time
48 interval groups with logistic regression analysis. Confounders are considered when the
49 change in stress score is >10% in the stratification for the respective parameter. A
50 multivariable regression analysis is performed, adjusting for confounders. A secondary
51 analysis is done by calculating the relative change in stress score before and after the
52 investigation and their corresponding 95% confidence interval (CI), with multivariable
53 regression analysis with confounders as described above.
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60 Secondary endpoints are reported unadjusted with corresponding 95% CI.

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3 A p-value of <0.05 is considered a significant difference. All analyses are done using STATA
4 16.1 or higher (StataCorp LLC, Texas, USA).
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8 **Interim analyses {21b}**

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10 No interim analyses are planned due to the low risk of the study intervention and an assumed
11 minimal burden to the patients.
12
13

14 **Methods in analysis to handle protocol non-adherence and any statistical methods to** 15 **handle missing data {20c}**

16 Postoperative complications requiring postoperative imaging in intubated patients unable to
17 complete the questionnaire and emergency imaging in extubated patients with relevant time
18 and personnel limitations are criteria for not performing the questionnaire. Furthermore,
19 questionnaires will not be performed in case the surgeon decides not to perform postoperative
20 imaging. These situations are defined as protocol deviations and these patients will be
21 excluded from analysis.
22

23 If only the data before postoperative imaging (only part of the questionnaire before
24 radiological examination fulfilled) are acquired and post-imaging data are missing, these
25 collected data will only be used in the baseline characteristics and not in the analysis of the
26 primary outcome. However, if the collected data include secondary outcomes, they will be
27 included into the secondary data analysis.
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34 **Plans to give access to the full protocol, participant level-data and statistical code {31c}**

35 We aim to publish the full study protocol in a peer-reviewed medical journal. Full access is
36 granted to the original protocol and participant level-data after consideration with the
37 corresponding author. The statistical code is written in STATA (StataCorp LLC, Texas,
38 USA) and available upon request.
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40
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44 **Oversight and monitoring**

45 No external monitoring is planned due to the low risk of the intervention (questionnaire) and
46 an assumed small burden for study participants. Internal monitoring by the project leader and
47 study coordinator is performed after including the first 10% of patients.
48
49
50

51 **Adverse event reporting and harms {22}**

52 Participation in the study includes only the completion of a questionnaire, in which we do not
53 expect to encounter (serious) adverse events ((S)AE). Nevertheless, if an (S)AE occurs, the
54 project leader and the sponsor will be notified within 24 hours and decide if immediate safety
55 and protective measures have to be taken during the conduct of the research project. The
56 Ethics Committee will be notified of these measures and of the underlying circumstances via
57 BASEC within 7 days.
58
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Frequency and plans for auditing trial conduct {23}

The department of neurosurgery of the USZ undergoes a research audit every five years to guarantee high quality of the conducted scientific research. Due to the low risk of the current study, no additional study specific audit is planned.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Substantial changes to the project set-up, the protocol, and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 using the BASEC system. The study team and nursing staff will be informed by oral information and email about important protocol changes.

Dissemination plans {31a}

The final decision on the publication of the results will be made by the sponsor (Luca Regli) and the project leader (Menno R. Germans). Authors of the publication are persons who conceived and planned the study or performed parts of the statistical analysis. Unless Luca Regli and Menno R. Germans decide otherwise, Lazar Tosic is the first author and Menno R. Germans is the last author. Joint first or last authorship may be decided if other investigators qualify appropriately by spending a large amount of time and effort on the study. All data belong to Luca Regli and Menno R. Germans, who will decide on authorship, order of authors, journals to be published, and partial results and aspects of the final analysis.

In consultation with Luca Regli and Menno R. Germans, parts of the study results may be analyzed separately by the participating investigators; for these analyses and publications, the first and last authors as well as the order of authorship will be determined by the sponsor, project leader and the principal investigator of the subproject.

Article summary

This project has been developed as an exploratory study to investigate whether postoperative imaging has an influence on patient well-being. As this is a hypothesis-creating study, we decided not to randomize patients beforehand and primarily aim to investigate potential factors of stress associated with postoperative imaging as well as potential differences caused by the interval between surgery and imaging. It is a patient-oriented study with patient-reported outcome measurements combined with clinical and radiological assessments.

Investigating the optimal time window for postoperative examinations may lead to an improvement of postoperative stress levels experienced by patients, which influences overall outcome. Factors causing additional postoperative stress are likely responsible for delayed

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2
3 recovery of neurosurgical patients. Reducing postoperative stress by establishing an optimal
4 time window for postoperative imaging is an important aspect of each neurosurgical patient's
5 journey from preoperative assessment to optimized postoperative recovery. (10)
6

7
8 . Future directions of study may emphasize on the comparison between similar groups (e.g.
9 by randomization) or on the investigation of factors which contribute to stress at the
10 postoperative radiological investigations. This study is conducted to establish a solid
11 foundation for such future studies.
12

13 **Strengths and limitations of this study**

14
15 The main strength of this study is its prospective and patient-oriented study design and a
16 large number of participants. The study is conducted as single centre study and this is the
17 main limitation. As this is a hypothesis-creating study, we decided not to randomize patients
18 beforehand and primarily aim to investigate potential factors of stress associated with
19 postoperative imaging as well as potential differences caused by the interval between surgery
20 and imaging
21
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24 **Trial status**

25
26 Patient recruitment started on September 20th 2020. Until February 5th 2022 we had recruited
27 120 participants. With the current inclusion rate, we expect to have the final data in January
28 2023.
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32 **Abbreviations**

| | |
|----|--|
| 33 | |
| 34 | |
| 35 | BASEC Business Administration System for Ethical Committees |
| 36 | |
| 37 | CRF Case report form |
| 38 | |
| 39 | FOPH Federal Office of Public Health |
| 40 | |
| 41 | HRA Human Research Act |
| 42 | |
| 43 | HRO Human research ordinance |
| 44 | |
| 45 | MRI Magnetic resonance imaging |
| 46 | |
| 47 | VAS Visual analogue scale |
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| 49 | CT Computed tomography |
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| 51 | AVM Arteriovenous malformation |
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| 53 | AVF Arteriovenous fistula |
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| 55 | USZ University Hospital Zurich |
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Declarations

Authors' contributions

Study concept and initiation: Menno R. Germans and Lazar Totic

Data collection: Marco Thoma, Stefanos Voglis, Delal Bektas, Anna-Sophie Hofer and Atina Pangalu

Data analysis: Lazar Totic, Menno R. Germans

Writing manuscript: Lazar Totic, Menno R. Germans

Critically reviewing manuscript: all authors

Funding

The project is funded by the Department of Neurosurgery of the University Hospital Zurich.

Availability of data and material

The data is encrypted and entered into Microsoft Access study-specific patient ID, which is password protected and stored on the hospital servers of the University Hospital Zurich.

Access to the data for the other colleagues in the department of Neurosurgery of the University Hospital Zurich can only be granted by the project leader and in case of participation in the study team.

Ethics approval and consent to participate

The institutional review board (Kantonale Ethikkommission Zürich) approved this study on 4th of August 2020 under case number: BASEC 2020-01590, Protocol version: 1.0; Protocol date: 25.06.2020.

Consent for publication

All participants gave their written consent for publication (Informed consent version 1.0; informed consent date 14.08.2020).

Competing interests

None to declare

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Figures

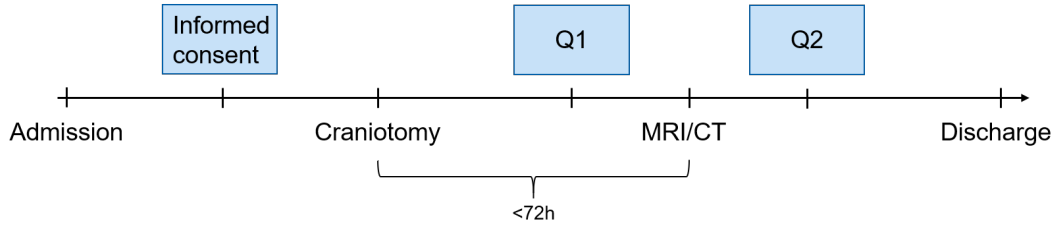
Figure 1: Participant timeline ; Q1: pre-imaging questionnaire assessing headache, nausea, and discomfort; Q2: post-imaging questionnaire assessing headache, nausea, discomfort, and timing of imaging

Figure 2: Visual analog scale (VAS) for headache

Figure 3: Visual analog scale (VAS) for nausea

Figure 4: Body Part Discomfort Scale

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For peer review only

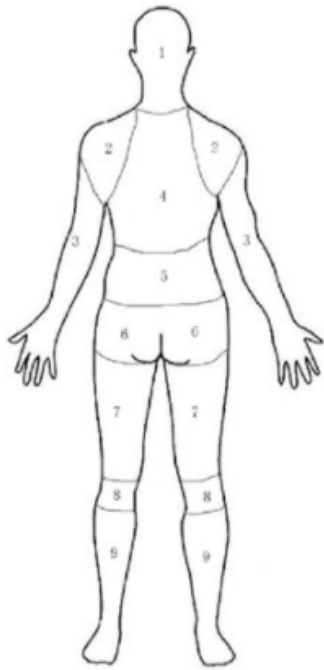
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| no | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | strongest | nausea |
| nausea | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | I can imagine |

For peer review only



1 Not uncomfortable 4 Very uncomfortable
2 Barely uncomfortable 5 Extremely uncomfortable
3 Quite uncomfortable

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| 1 Head and neck | <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 |
| 2 Shoulder | <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 |
| 3 Arm | <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 |
| 4 Middle back | <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 |
| 5 Low back | <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 |
| 6 Buttock | <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 |
| 7 Thigh | <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 |
| 8 Knee | <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 |
| 9 Leg and foot | <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 |

Peer review only

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BMJ Open

Evaluation of patient STress level caused by radiological Investigations in early Postoperative phase After CRANIOTomy (IPAST-CRANIO): protocol of a Swiss prospective cohort study

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| | |

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Manuscripts

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4 **Evaluation of patient STress level caused by radiological Investigations in early**
5 **Postoperative phase After CRANIOTomy (IPAST-CRANIO): protocol of a Swiss**
6 **prospective cohort study**
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Abstract

Introduction:

Postoperative imaging after neurosurgical interventions is usually performed in the first 72 hours after surgery to provide an accurate assessment of postoperative resection status. Patient frequently report that early postoperative examination after craniotomy for tumor and vascular procedures is associated with distress, exertion, nausea, and pain. Delayed postoperative imaging (between 36 and 72 hours postoperatively) may have an advantage regarding psychological and physical stress compared to early imaging. The goal of this study is to evaluate and determine the optimal time frame for postoperative imaging with MRI and CT in terms of medical and neuroradiological implications and patient's subjective stress level.

Methods and Analysis

Data will be prospectively collected from all patients aged 18 to 80 years who receive postoperative MRI or CT imaging following a craniotomy for resection of a cerebral tumor (benign and malignant) or vascular surgery. Participants have to complete questionnaires containing visual analogue scores for headache and nausea (VAS), Body Part Discomfort score and a single question addressing subjective preference of timing of postoperative imaging after craniotomy. The primary endpoint of the study is the difference in subjective stress due to imaging studies after craniotomy, measured just before and after postoperative MRI or CT with the above mentioned instruments. Subjective stress is defined as a combination of the scores VAS pain, VAS nausea, and $0.5 \times$ Body Part Discomfort score.

This study determines whether proper timing of postoperative imaging can improve patient satisfaction and reduce pain, stress and discomfort caused by postoperative imaging. Factors causing additional postoperative stress are likely responsible for delayed recovery of neurosurgical patients.

Ethics and Dissemination

The institutional review board (Kantonale Ethikkommission Zürich) approved this study on 4 August 2020 under case number BASEC 2020-01590. This trial has also been registered in Clinical Trials under ClinicalTrials.gov ID: NCT05112575.

Article summary

This project has been developed as an exploratory study to investigate whether postoperative imaging has an influence on patient well-being. As this is a hypothesis-creating study, we decided not to randomize patients beforehand and primarily aim to investigate potential factors of stress associated with postoperative imaging as well as potential differences caused by the interval between surgery and imaging. It is a patient-oriented study with patient-reported outcome measurements combined with clinical and radiological assessments.

Investigating the optimal time window for postoperative examinations may lead to an improvement of postoperative stress levels experienced by patients, which influences overall outcome. Factors causing additional postoperative stress are likely responsible for delayed recovery of neurosurgical patients. Reducing postoperative stress by establishing an optimal time window for postoperative imaging is an important aspect of each neurosurgical patient's journey from preoperative assessment to optimized postoperative recovery. (1)

. Future directions of study may emphasize on the comparison between similar groups (e.g. by randomization) or on the investigation of factors which contribute to stress at the postoperative radiological investigations. This study is conducted to establish a solid foundation for such future studies.

Strengths and limitations of this study

The main strength of this study is its prospective and patient-oriented study design and a large number of participants. The study is conducted as single centre study and this is the main limitation. As this is a hypothesis-creating study, we decided not to randomize patients beforehand and primarily aim to investigate potential factors of stress associated with postoperative imaging as well as potential differences caused by the interval between surgery and imaging

Keywords

Magnetic resonance imaging – computed tomography - craniotomy – postoperative imaging

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers.

The order of the items has been modified to group similar items (see <http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/>)

| | |
|-----------|---|
| Title {1} | Evaluation of patient stress level caused by radiological investigations in early postoperative phase after craniotomy (IPAST-CRANIO) |
|-----------|---|

| | |
|---|--|
| Trial registration {2a and 2b}. | <p>The institutional review board (Kantonale Ethikkommission Zürich) approved this study on 4 August 2020 under case number: BASEC 2020-01590.</p> <p>This trial has also been registered in Clinical Trials under ClinicalTrials.gov ID: NCT05112575.</p> |
| Protocol version {3} | 1.0, 25.06.2020 |
| Funding {4} | This research is financed by the Department of Neurosurgery, University Hospital Zurich, Switzerland. |
| Author details {5a} | <p>Lazar Tomic, MD</p> <p>Marco Thoma, cand. MScN</p> <p>Stefanos Voglis, MD</p> <p>Anna-Sophie Hofer, MD, PhD</p> <p>A. Pangalu, MD</p> <p>Luca Regli, MD</p> <p>Menno R. Germans, MD, PhD</p> |
| Name and contact information for the trial sponsor {5b} | <p>Prof. Dr. Luca Regli</p> <p>E-Mail: luca.regli@usz.ch</p> <p>Tel.: +4144255992</p> |
| Role of sponsor {5c} | Design; management, analysis and interpretation of data; critically reviewing the manuscript; and the decision to submit the report for publication. |

Background and rationale {6a}

Magnetic resonance imaging (MRI) after neurosurgical resection of a cerebral tumor is usually performed in the first 72 hours after surgery. (2-5) accurate assessment of early postoperative resection status of brain tumors is mandatory for further treatment planning, e.g., delineation of the radiation field during radiotherapy, or reoperation for significant residual tumor. (6) Various MRI-sequences provide information on tumor size and location, as well as additional insight into secondary phenomena such as edema, hemorrhage, infarct,

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3 necrosis, and signs of increased intracranial pressure. (2, 4, 6, 7) The 72 hours time window
4 is crucial for accurate assessment of resection status and is additionally used for quality
5 control of neurosurgical procedures. (8) Postoperative MRI performed later than 72 hours
6 after surgery can lead to false positive contrast enhancement due to absorption of contrast in
7 the surgical area which can complicate the assessment of resection status. (2, 7) Postsurgical
8 repair mechanisms at the resection site resulting from hypervascularization and disruption of
9 the blood-brain barrier are probably responsible for this delayed enhancement. (8)
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13 The potential advantages of early imaging (within 36 hours after surgery) are better
14 radiological assessment of the surgical site and earlier diagnosis of postoperative
15 complications, such as infarcts, postoperative bleeding or edema. This may help improve the
16 postoperative management of patients with complications. Moreover, earlier information
17 about the outcome of surgery could also lead to psychological relief for patients in the early
18 postoperative period. Disadvantages of early postoperative examinations after craniotomy are
19 frequently reported by patients and include distress, exertion, nausea, and pain during and
20 after the examination. As such, psychological and physical patient stress could be a potential
21 disadvantage of early (within 36 hours after surgery) MRI examination. An alternative image
22 modality is computed tomography (CT), which may be less stressful for patients as it takes
23 only 5 to 10 minutes to complete the scan and patients do not have to lie in a narrow scanner
24 as for MRI examinations. However, with this modality the postoperative resection status
25 cannot be reliably assessed. To our knowledge, no previous literature has been published
26 which addressed stress factors during postoperative imaging. To our opinion, a more patient-
27 centered design of the early postoperative course including timing of postoperative imaging
28 studies requires the investigation of patient stress levels associated with postoperative
29 imaging performed at different time intervals from surgery. With the optimization of the
30 postoperative time window for MRI and CT examinations we aim to improve psychological
31 and physical patient stress, which may have a positive influence on early recovery.
32 Additionally, establishing an optimal time window for postoperative MRI imaging will help
33 in scheduling the examination before the elective surgical treatment. This will have a positive
34 impact on preparing patients, radiology employees, nurses and physicians for a smooth and
35 easy transport to and from the MRI examination.
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46 **Objectives {6a}**

47 The goal of this study is to assess whether early imaging with MRI (within 36 hours) after
48 craniotomy has a different impact on patient stress compared to delayed imaging (between 36
49 and 72 hours). Secondly, we aim to assess whether there is a difference in patient stress level
50 between postoperative MRI and CT performed within 72 hours postoperatively.
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53 The authors hypothesize that delayed MRI imaging after craniotomy is more comfortable for
54 patients without having negative implications on the validity and reliability of radiological
55 assessments compared to imaging performed within 36 hours. Secondly, we hypothesize that
56 postoperative MRI is more stressful for patients than postoperative CT.
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Trial design {8}

The IPAST-CRANIO study (Evaluation of patient Stress level caused by radiological Investigations in early Postoperative phase After CRANIOTomy) is a patient-oriented, prospective, exploratory cohort study.

Methods: Participants, interventions and outcomes

Study setting {9}

Data will be collected from patients between 18 and 80 years old who receive MRI or CT follow-up studies after craniotomy for resection of a space occupying lesion (benign or malignant) or vascular procedure at the Department of Neurosurgery at the University Hospital Zurich.

Eligibility criteria {10}

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- Written consent of the patient
- Age between 18 and 80 years
- Planned supra- or infratentorial (partial) resection of space occupying lesion (benign or malignant) or vascular neurosurgical procedure (clipping of an aneurysm, resection of an arteriovenous malformation/fistula, resection of cavernoma)
- Planned MRI or CT follow-up within 72 hours after surgery

The presence of any of the following exclusion criteria will lead to exclusion of the participant:

- No informed consent
- Surgery involving only one burr hole (e.g. biopsy) instead of craniotomy
- Not able to fill out the questionnaires due to cognitive impairment or aphasia
- Not German or English speaking
- Contraindication for MRI/CT examination
- No postoperative MRI or CT examination planned within 72 hours after surgery

Patient and Public Involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Who will take informed consent? {26a}

Patients will be informed verbally and in writing about the study by members of the study team. The information will be given at least one day before the surgical procedure to ensure enough time to consider participation. We emphasize that participation in the study does not

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3 impose a significant additional burden on patients as only short questionnaires need to be
4 completed which do not entail any significant risks or unreasonable questions.
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8 **Additional consent provisions for collection and use of participant data and biological** 9 **specimens {26b}**

10 Furthermore, patients will be informed and educated in detail about other aspects:
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- 12 • The intended further use of the non-genetic data for research purposes;
- 13 • Their right to refuse or withdraw consent at any time without justification;
- 14 • Their right to be informed of the results affecting their health and their right to waive this
15 information;
- 16 • The measures taken to protect personal data;
- 17 • The possibility of sharing the personal data with third parties for research purposes.
- 18 • The collection of patients' consent will take place after the study has been approved by
19 the Ethics Committee.
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26 **Interventions**

27 **Explanation for the choice of comparators {6b}**

28 The authors hypothesize that the optimal period for postoperative imaging is 36 to 72 hours
29 and therefore decided to include the early time frame (within 36 hours) as an adequate
30 comparator. The authors will also compare the outcomes between the group undergoing
31 postoperative CT and the group undergoing postoperative MRI.
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35 **Intervention description {11a}**

36 In general, all patients in our institution receive postoperative imaging within the first 72
37 hours after a craniotomy for a space-occupying lesion or vascular procedure. The study
38 intervention includes the completion of a questionnaire right before and after the
39 postoperative radiological investigation (Figure 1, see supplementary data). Patients are
40 divided in two groups depending on the time interval between end of surgery and radiological
41 investigation: late group (completing the questionnaire 36 to 72 hours after surgery) and early
42 group (completing the questionnaire within 36 hours after surgery). The time intervals to the
43 radiological investigation are assigned by coincidence and the patients are not randomized
44 into any group. The exact time interval until examination depends on various factors, e.g.:
45 capacity of the department of neuroradiology or weekday of surgery (patients operated on
46 Friday are more likely to receive postoperative imaging on Monday; patients operated on
47 Thursday are most likely receive it on Friday) and patient condition (early imaging will more
48 likely be performed in suspected postoperative complications). We decided to use this way of
49 defining the comparators as we a primariily interested in examining potential differences
50 between groups, rather than assessing causality between delayed imaging and stress level.
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57 The questionnaire consists of visual analog scale (VAS) for headache, visual analog scale
58 (VAS) for nausea, and Body Part Discomfort Scale (Figures 2, 3 and 4). At the end of the
59 questionnaire, patients will be asked to answer the following question:
60

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3 In your opinion, should the MRI and/or CT scan have been performed earlier or later? The
4 possible answers are:

- 5
6
- 7 ○ Yes, earlier;
 - 8 ○ Yes, later;
 - 9 ○ No, I am satisfied with the timing of the exam.

10 The authors have chosen these scales because they are validated and simple to understand and
11 register. The completion of each questionnaire will take 5 to 10 minutes, and the burden for
12 each patient is assumed to be low as the questionnaires do not contain any unreasonable
13 questions.
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17 **Criteria for discontinuing or modifying allocated interventions {11b}**

18 Although patients might have signed the informed consent situations that do not allow for
19 completion of the questionnaires can occur. Reasons include postoperative complications
20 leading to imaging in intubated patients, emergency imaging in extubated patients, , or the
21 neurosurgeon's decision not to perform postoperative imaging due to case-specific
22 considerations. These patients will be excluded from analysis and the reason for not
23 completing the questionnaire will be registered.
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27 **Strategies to improve adherence to interventions {11c}**

28 This study is implemented in close and intensive collaboration with nursing staff and
29 supported by residents, medical students and administrative staff. Through this collaboration
30 the study team has managed to create sufficient resources ensuring a high and optimal
31 adherence to the intervention.
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35 **Relevant concomitant care permitted or prohibited during the trial {11d}**

36 None, the interval to radiological investigation will not be delayed due to completion of the
37 questionnaire.
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41 **Provisions for post-trial care {30}**

42 Participants will be informed about the results by an information letter, if interested. The
43 scheduling of future postoperative imaging will be planned based on this study's results.
44
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46 **Outcomes {12}**

47 The primary endpoint of the study is the difference in subjective stress after craniotomy
48 measured right before and after postoperative MRI or CT imaging with the mentioned
49 instruments. Subjective stress is evaluated as a combination of the scores VAS pain, VAS
50 nausea, and 0.5* Body Part Discomfort score (Figures 2, 3 and 4). A minimum score of 4.5
51 and a maximum score of 42.5 can be achieved.
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54 The secondary endpoints of the study are divided into two groups:

55 1. Patient specific secondary endpoint:

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- 58 • patient interpretation of whether MRI follow-up was performed at the correct interval.
- 59
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2. Radiology specific secondary endpoints:

- residual tumor on MRI.
- contrast enhancement on MRI (postoperative reactive change, not tumor specific).
- significant post-operative bleeding.
- Infarction.
- residual perfusion of the aneurysm or AVM/AVF remnant.

Participant timeline (Figure 1) {13}

Patients are screened on the hospital admission day by the study team and informed consent is taken if inclusion criteria are fulfilled and if no exclusion criteria are met. Questionnaires are completed by patients immediately before and after postoperative MRI or CT imaging. The study is finished for each patient after having completed the post-investigational questionnaire. If either or both questionnaire(s) cannot be completed, the patient's study participating is finished after the radiological investigation. Radiological findings are assessed and documented in writing by a neuroradiologist according to local guidelines.

Sample size {14}

A sample measurement of VAS scores in 100 patients with craniotomy for tumour resection in 2019 resulted in a mean score of 1.8 (VAS pain) and 0.8 (VAS nausea). Because there was no baseline data for the Body Part Discomfort score, it was equated to the percentage of VAS pain per patient. This resulted in an average Body Part Discomfort score of 12.3 points. For calculating the total score, the VAS-scores and half of the points from the Body Part Discomfort score are used. The total mean score of all three measurements then becomes 13.6 (standard deviation 5.4). To measure an expected change of one third for the separate scores with a power of 80% and a type I error of 5%, a total of 224 patients are required for the study. To correct for any loss to follow-up, we will include 230 patients in this study.

Recruitment {15}

The study team screens all the patients on the admission day based on demographics, diagnosis and planned operation. All adult patients receiving craniotomy for a space occupying lesion or vascular indications are asked to participate in the study.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Data will be collected from all patients aged 18 to 80 years who receive postoperative MRI or CT follow-up after craniotomy for resection of a cerebral space-occupying lesion (benign and malignant) or vascular procedure using a questionnaire. Radiological findings are assessed and documented in writing by a neuroradiologist according to local guidelines.

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3 The CRF collects the following information and scores:
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- 5 - Demographic data of patients (sex, age)
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- 7 - Localization of craniotomy (side, supra- or infratentorial, lobe and region)
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- 9 - Time interval (in hours and postoperative day) between end of surgery and start of MRI or
- 10 CT scan
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- 12 - Indications for post operative imaging as per the surgeon
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- 14 - Neuroradiology reports of postoperative imaging examinations
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- 16 - Patient related criteria:
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 - 18 • Visual analog scale (VAS) for headache (Figure 2).(9)
 - 19 • VAS for nausea (Figure 3).(9)
 - 20 • Body Part Discomfort Scale (Figure 4)(10).
 - 21
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24 At the end of the second questionnaire, patients will be asked to answer the following
25 question:
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- 27 - In your opinion, should the MRI and/or CT scan have been performed earlier or later? The
28 possible answers are:
29
 - 30 ○ Yes, earlier;
 - 31 ○ Yes, later;
 - 32 ○ No, I am satisfied with the timing of the exam.
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36 The radiological criteria that will be examined are as follows:
37

- 38 - Location of tumor (supra- or infratentorial, left or right)
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- 40 - Tumor remnant on MRI
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- 42 - Contrast enhancement on MRI (postoperative reactive change, not tumor-specific)
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- 44 - Significant postoperative hemorrhage
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- 46 - Postoperative infarction
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- 48 - Residual perfusion of the aneurysm or AVM/AVF remnant
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56 **Plans to promote participant retention and complete follow-up {18b}**

57 In this study, patients will complete a questionnaire before and after postoperative
58 radiological examination. At the morning rounds, nursing staff is informed about patients
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3 who are planned for radiological examination and who are included in the study. When the
4 nursing staff is informed about the exact time for the MRI or CT, the attending nurse
5 (supported by a resident or a medical student if necessary) gives the questionnaire to the
6 patient. The nurse is continuously reminded for this step, thanks to a comment in the digital
7 patient report system (KISIM). Nursing staff and medical staff will monitor the completion of
8 the questionnaires and can support at any time.
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13 **Data management {19}**

14 Source data are available as paper questionnaires from patients and as digital documentation
15 in the hospital-wide patient report system (KISIM) for clinical and radiological information.
16 These data are pseudonymized, coded and stored in the form of the coded data in two
17 Microsoft Access tables. One table contains the patient's hospital identification number, date
18 of birth, and study number. The second Microsoft Access table contains all coded study data
19 and patients are identified by study number only. Both tables are protected with passwords
20 and are stored in a secured folder and are only accessible for study team members. Completed
21 questionnaires are stored in a closed cabinet (available in research office and only accessible
22 to the Project Leader of the study).
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29 **Confidentiality {27}**

30 Personal and medical data will be collected for this study. When data is collected for study
31 purposes, the data is pseudonymized and coded. The coding ensures that all reference data
32 that would reveal the identity of a patient (name, date of birth) is deleted and replaced by a
33 key. The list of keys always remains in the institution/hospital. In the case of a publication,
34 the summarized data cannot be traced back to an individual person. The name of a patient
35 will never appear on the internet or in any publication.
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41 **17. Data storage details**

42 The generation, transfer, storage, and analysis of health data within the scope of this project is
43 carried out in strict compliance with the current legal provisions for data in Swiss Protection
44 and is carried out according to the HRO regulation Art. 5.
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47 All persons who have access to patient data within the scope of the study are subject to the
48 obligation of confidentiality.
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50 It is possible that the study will be reviewed by the ethics committee or by the institution that
51 initiated the study. The investigator may have to disclose personal and medical data for such
52 controls. All persons must maintain absolute confidentiality.
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Statistical methods

Statistical methods for primary and secondary outcomes {20a}

For data analysis, patients are being divided into 2 groups based on predefined time intervals:

1. early imaging: within 36 hours postoperatively.
2. late imaging: between 36 and 72 hours postoperatively.

A second analysis is performed, dividing patients into the following groups:

1. early imaging: on the same day of surgery (day 0) or 1st postoperative day.
2. late imaging: on the 2nd or 3rd postoperative day.

A third analysis will be performed, dividing the patients based on the radiological examination performed (MRI or CT).

Descriptive data will be investigated for a normal distribution. In case of a normal distribution, results will be presented as means with standard deviations and groups compared by Chi-square tests. If not, the results will be presented as medians with interquartile ranges and results of a non-parametric (Fisher's exact test) will be reported. Results of pre- and post-imaging questionnaires are compared with the paired t-test, or Wilcoxon signed rank test in case of a non-normal distribution of data. The primary outcome is assessed by subtracting the mean subjective stress score before the investigation from the score after the investigation. Crude and adjusted stress score differences are calculated in relation to the predefined time interval groups with logistic regression analysis. Confounders are considered when the change in stress score is >10% in the stratification for the respective parameter. A multivariable regression analysis is performed, adjusting for confounders. A secondary analysis is done by calculating the relative change in stress score before and after the investigation and their corresponding 95% confidence interval (CI), with multivariable regression analysis with confounders as described above.

Secondary endpoints are reported unadjusted with corresponding 95% CI.

A p-value of <0.05 is considered a significant difference. All analyses are done using STATA 16.1 or higher (StataCorp LLC, Texas, USA).

Interim analyses {21b}

No interim analyses are planned due to the low risk of the study intervention and an assumed minimal burden to the patients.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Postoperative complications requiring postoperative imaging in intubated patients unable to complete the questionnaire and emergency imaging in extubated patients with relevant time and personnel limitations are criteria for not performing the questionnaire. Furthermore, questionnaires will not be performed in case the surgeon decides not to perform postoperative imaging. These situations are defined as protocol deviations and these patients will be excluded from analysis.

If only the data before postoperative imaging (only part of the questionnaire before radiological examination fulfilled) are acquired and post-imaging data are missing, these collected data will only be used in the baseline characteristics and not in the analysis of the primary outcome. However, if the collected data include secondary outcomes, they will be included into the secondary data analysis.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

We aim to publish the full study protocol in a peer-reviewed medical journal. Full access is granted to the original protocol and participant level-data after consideration with the corresponding author. The statistical code is written in STATA (StataCorp LLC, Texas, USA) and available upon request.

Oversight and monitoring

No external monitoring is planned due to the low risk of the intervention (questionnaire) and an assumed small burden for study participants. Internal monitoring by the project leader and study coordinator is performed after including the first 10% of patients.

Adverse event reporting and harms {22}

Participation in the study includes only the completion of a questionnaire, in which we do not expect to encounter (serious) adverse events ((S)AE). Nevertheless, if an (S)AE occurs, the project leader and the sponsor will be notified within 24 hours and decide if immediate safety and protective measures have to be taken during the conduct of the research project. The Ethics Committee will be notified of these measures and of the underlying circumstances via BASEC within 7 days.

Frequency and plans for auditing trial conduct {23}

The department of neurosurgery of the USZ undergoes a research audit every five years to guarantee high quality of the conducted scientific research. Due to the low risk of the current study, no additional study specific audit is planned.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Substantial changes to the project set-up, the protocol, and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 using the BASEC system. The study team and nursing staff will be informed by oral information and email about important protocol changes.

Ethics and dissemination {31a}

The final decision on the publication of the results will be made by the sponsor (Luca Regli) and the project leader (Menno R. Germans). Authors of the publication are persons who conceived and planned the study or performed parts of the statistical analysis. Unless Luca Regli and Menno R. Germans decide otherwise, Lazar Tosic is the first author and Menno R. Germans is the last author. Joint first or last authorship may be decided if other investigators qualify appropriately by spending a large amount of time and effort on the study. All data belong to Luca Regli and Menno R. Germans, who will decide on authorship, order of authors, journals to be published, and partial results and aspects of the final analysis.

In consultation with Luca Regli and Menno R. Germans, parts of the study results may be analyzed separately by the participating investigators; for these analyses and publications, the first and last authors as well as the order of authorship will be determined by the sponsor, project leader and the principal investigator of the subproject.

The institutional review board (Cantonal Ethics Committee Zürich) approved this study on 4th of August 2020 under case number: BASEC 2020-01590, Protocol version: 1.0; Protocol date: 25.06.2020.

Trial status

Patient recruitment started on September 20th 2020. Until February 5th 2022 we had recruited 120 participants. With the current inclusion rate, we expect to have the final data in January 2023.

Abbreviations

BASEC Business Administration System for Ethical Committees

CRF Case report form

| | |
|-------------|---------------------------------|
| FOPH | Federal Office of Public Health |
| HRA | Human Research Act |
| HRO | Human research ordinance |
| MRI | Magnetic resonance imaging |
| VAS | Visual analogue scale |
| CT | Computed tomography |
| AVM | Arteriovenous malformation |
| AVF | Arteriovenous fistula |
| USZ | University Hospital Zurich |

Declarations

Authors' contributions

Study concept and initiation: Menno R. Germans, Lazar Tomic and Luca Regli

Data collection: Marco Thoma, Stefanos Voglis, Delal Bektas, Anna-Sophie Hofer and Atina Pangalu

Data analysis: Lazar Tomic, Menno R. Germans

Writing manuscript: Lazar Tomic, Menno R. Germans

Critically reviewing manuscript: all authors

Funding

The project is funded by the Department of Neurosurgery of the University Hospital Zurich.

Availability of data and material

The data is encrypted and entered into Microsoft Access study-specific patient ID, which is password protected and stored on the hospital servers of the University Hospital Zurich.

Access to the data for the other colleagues in the department of Neurosurgery of the University Hospital Zurich can only be granted by the project leader and in case of participation in the study team.

Ethics approval and consent to participate

The institutional review board (Kantonale Ethikkommission Zürich) approved this study on 4th of August 2020 under case number: BASEC 2020-01590, Protocol version: 1.0; Protocol date: 25.06.2020.

Consent for publication

All participants gave their written consent for publication (Informed consent version 1.0; informed consent date 14.08.2020).

Competing interests

None to declare

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Figures

Figure 1: Participant timeline ; Q1: pre-imaging questionnaire assessing headache, nausea, and discomfort; Q2: post-imaging questionnaire assessing headache, nausea, discomfort, and timing of imaging

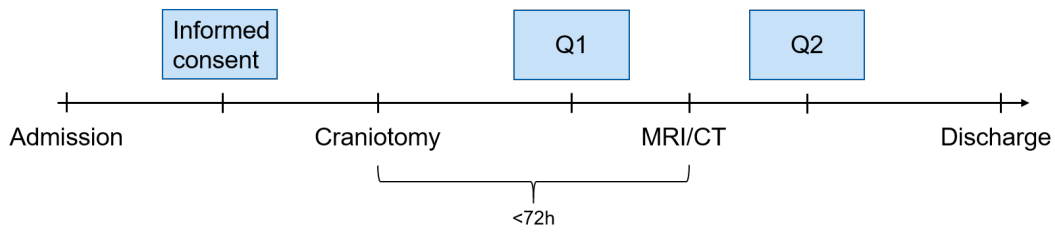
Figure 2: Visual analog scale (VAS) for headache

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Figure 3: Visual analog scale (VAS) for nausea

Figure 4: Body Part Discomfort Scale

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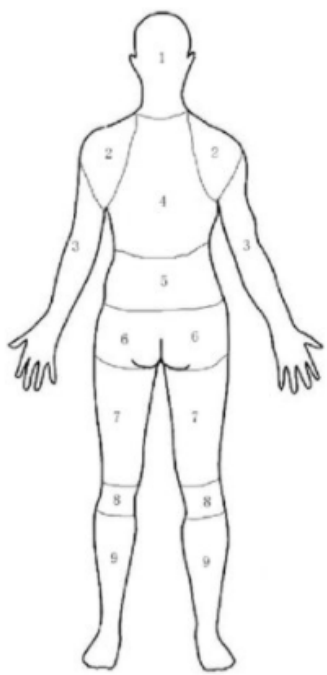
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1 Not uncomfortable 4 Very uncomfortable
 2 Barely uncomfortable 5 Extremely uncomfortable
 3 Quite uncomfortable

1 Head and neck 1 2 3 4 5

2 Shoulder 1 2 3 4 5

3 Arm 1 2 3 4 5

4 Middle back 1 2 3 4 5

5 Low back 1 2 3 4 5

6 Buttock 1 2 3 4 5

7 Thigh 1 2 3 4 5

8 Knee 1 2 3 4 5

9 Leg and foot 1 2 3 4 5

Peer review only

BMJ Open

Evaluation of patient STress level caused by radiological Investigations in early Postoperative phase After CRANIOTomy (IPAST-CRANIO): protocol of a Swiss prospective cohort study

| | |
|---------------------------------|--|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2022-061452.R2 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 24-May-2022 |
| Complete List of Authors: | Tosic, Lazar; UniversitätsSpital Zürich, Neurosurgery Thoma, Marco; Department of Neurosurgery, University Hospital Zurich, Switzerland Voglis, Stefanos; University Hospital Zurich, Neurosurgery Hofer, Anna Sophie; Department of Neurosurgery, University Hospital Zurich, Switzerland Bektas, Delal; Department of Neurosurgery, University Hospital Zurich, Switzerland Pangalu, Athina; Department of Neurosurgery, University Hospital Zurich, Switzerland Regli, Luca; University Hospital Zurich, Neurosurgery Germans, Menno; University Hospital Zurich, Neurosurgery |
| Primary Subject Heading: | Surgery |
| Secondary Subject Heading: | Patient-centred medicine, Qualitative research, Radiology and imaging |
| Keywords: | Computed tomography < RADIOLOGY & IMAGING, NEUROSURGERY, Magnetic resonance imaging < RADIOLOGY & IMAGING |
| | |

SCHOLARONE™
Manuscripts

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4 **Evaluation of patient STress level caused by radiological Investigations in early**
5 **Postoperative phase After CRANIOTomy (IPAST-CRANIO): protocol of a Swiss**
6 **prospective cohort study**
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11 Lazar Tomic^{1,2}, MD; Marco Thoma¹, cand. MScN; Stefanos Voglis^{1,2}, MD; Anna-Sophie
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13 R. Germans^{1,2}, MD, PhD
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Abstract

Introduction:

Postoperative imaging after neurosurgical interventions is usually performed in the first 72 hours after surgery to provide an accurate assessment of postoperative resection status. Patient frequently report that early postoperative examination after craniotomy for tumor and vascular procedures is associated with distress, exertion, nausea, and pain. Delayed postoperative imaging (between 36 and 72 hours postoperatively) may have an advantage regarding psychological and physical stress compared to early imaging. The goal of this study is to evaluate and determine the optimal time frame for postoperative imaging with MRI and CT in terms of medical and neuroradiological implications and patient's subjective stress level.

Methods and Analysis

Data will be prospectively collected from all patients aged 18 to 80 years who receive postoperative MRI or CT imaging following a craniotomy for resection of a cerebral tumor (benign and malignant) or vascular surgery. Participants have to complete questionnaires containing visual analogue scores for headache and nausea (VAS), Body Part Discomfort score and a single question addressing subjective preference of timing of postoperative imaging after craniotomy. The primary endpoint of the study is the difference in subjective stress due to imaging studies after craniotomy, measured just before and after postoperative MRI or CT with the above mentioned instruments. Subjective stress is defined as a combination of the scores VAS pain, VAS nausea, and $0.5 \times$ Body Part Discomfort score.

This study determines whether proper timing of postoperative imaging can improve patient satisfaction and reduce pain, stress and discomfort caused by postoperative imaging. Factors causing additional postoperative stress are likely responsible for delayed recovery of neurosurgical patients.

Ethics and Dissemination

The institutional review board (Kantonale Ethikkommission Zürich) approved this study on 4 August 2020 under case number BASEC 2020-01590. The authors are planning to publish the data of this study in a peer-reviewed paper. The sponsor (Luca Regli) and the project leader (Menno R. Germans) will make the final decision on the publication of the results. The data that support the findings of this study are available on request from the corresponding author Lazar Tosic. The data are not publicly available due to privacy/ethical restrictions.

Registration

This trial has also been registered in Clinical Trials under ClinicalTrials.gov ID: NCT05112575.

Strengths and limitations of this study

The main strength of this study is its prospective and patient-oriented study design and a large number of participants. The study is conducted as single centre study and this is the main limitation. As this is a hypothesis-creating study, we decided not to randomize patients beforehand and primarily aim to investigate potential factors of stress associated with postoperative imaging as well as potential differences caused by the interval between surgery and imaging

Keywords

Magnetic resonance imaging – computed tomography - craniotomy – postoperative imaging

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers.

The order of the items has been modified to group similar items (see <http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/>)

| | |
|---------------------------------|---|
| Title {1} | Evaluation of patient stress level caused by radiological investigations in early postoperative phase after craniotomy (IPAST-CRANIO) |
| Trial registration {2a and 2b}. | The institutional review board (Kantonale Ethikkommission Zürich) approved this study on 4 August 2020 under case number: BASEC 2020-01590. This trial has also been registered in Clinical Trials under ClinicalTrials.gov ID: NCT05112575. |
| Protocol version {3} | 1.0, 25.06.2020 |
| Funding {4} | This research is financed by the Department of Neurosurgery, University Hospital Zurich, Switzerland. |
| Author details {5a} | Lazar Tosic, MD Marco Thoma, cand. MScN Stefanos Voglis, MD |

| | |
|---|--|
| | Anna-Sophie Hofer, MD, PhD A. Pangalu, MD Luca Regli, MD Menno R. Germans, MD, PhD |
| Name and contact information for the trial sponsor {5b} | Prof. Dr. Luca Regli E-Mail: luca.regli@usz.ch Tel.: +4144255992 |
| Role of sponsor {5c} | Design; management, analysis and interpretation of data; critically reviewing the manuscript; and the decision to submit the report for publication. |

Background and rationale {6a}

Magnetic resonance imaging (MRI) after neurosurgical resection of a cerebral tumor is usually performed in the first 72 hours after surgery. (2-5) accurate assessment of early postoperative resection status of brain tumors is mandatory for further treatment planning, e.g., delineation of the radiation field during radiotherapy, or reoperation for significant residual tumor. (6) Various MRI-sequences provide information on tumor size and location, as well as additional insight into secondary phenomena such as edema, hemorrhage, infarct, necrosis, and signs of increased intracranial pressure. (2, 4, 6, 7) The 72 hours time window is crucial for accurate assessment of resection status and is additionally used for quality control of neurosurgical procedures. (8) Postoperative MRI performed later than 72 hours after surgery can lead to false positive contrast enhancement due to absorption of contrast in the surgical area which can complicate the assessment of resection status. (2, 7) Postsurgical repair mechanisms at the resection site resulting from hypervascularization and disruption of the blood-brain barrier are probably responsible for this delayed enhancement. (8)

The potential advantages of early imaging (within 36 hours after surgery) are better radiological assessment of the surgical site and earlier diagnosis of postoperative complications, such as infarcts, postoperative bleeding or edema. This may help improve the postoperative management of patients with complications. Moreover, earlier information about the outcome of surgery could also lead to psychological relief for patients in the early postoperative period. Disadvantages of early postoperative examinations after craniotomy are frequently reported by patients and include distress, exertion, nausea, and pain during and after the examination. As such, psychological and physical patient stress could be a potential disadvantage of early (within 36 hours after surgery) MRI examination. An alternative image modality is computed tomography (CT), which may be less stressful for patients as it takes

only 5 to 10 minutes to complete the scan and patients do not have to lie in a narrow scanner as for MRI examinations. However, with this modality the postoperative resection status cannot be reliably assessed. To our knowledge, no previous literature has been published which addressed stress factors during postoperative imaging. To our opinion, a more patient-centered design of the early postoperative course including timing of postoperative imaging studies requires the investigation of patient stress levels associated with postoperative imaging performed at different time intervals from surgery. With the optimization of the postoperative time window for MRI and CT examinations we aim to improve psychological and physical patient stress, which may have a positive influence on early recovery. Additionally, establishing an optimal time window for postoperative MRI imaging will help in scheduling the examination before the elective surgical treatment. This will have a positive impact on preparing patients, radiology employees, nurses and physicians for a smooth and easy transport to and from the MRI examination.

Objectives {6a}

The goal of this study is to assess whether early imaging with MRI (within 36 hours) after craniotomy has a different impact on patient stress compared to delayed imaging (between 36 and 72 hours). Secondly, we aim to assess whether there is a difference in patient stress level between postoperative MRI and CT performed within 72 hours postoperatively.

The authors hypothesize that delayed MRI imaging after craniotomy is more comfortable for patients without having negative implications on the validity and reliability of radiological assessments compared to imaging performed within 36 hours. Secondly, we hypothesize that postoperative MRI is more stressful for patients than postoperative CT.

Trial design {8}

The IPAST-CRANIO study (Evaluation of patient STress level caused by radiological Investigations in early Postoperative phase After CRANIOtomy) is a patient-oriented, prospective, exploratory cohort study.

Methods: Participants, interventions and outcomes

Study setting {9}

Data will be collected from patients between 18 and 80 years old who receive MRI or CT follow-up studies after craniotomy for resection of a space occupying lesion (benign or malignant) or vascular procedure at the Department of Neurosurgery at the University Hospital Zurich.

Eligibility criteria {10}

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- Written consent of the patient
- Age between 18 and 80 years

- Planned supra- or infratentorial (partial) resection of space occupying lesion (benign or malignant) or vascular neurosurgical procedure (clipping of an aneurysm, resection of an arteriovenous malformation/fistula, resection of cavernoma)
- Planned MRI or CT follow-up within 72 hours after surgery

The presence of any of the following exclusion criteria will lead to exclusion of the participant:

- No informed consent
- Surgery involving only one burr hole (e.g. biopsy) instead of craniotomy
- Not able to fill out the questionnaires due to cognitive impairment or aphasia
- Not German or English speaking
- Contraindication for MRI/CT examination
- No postoperative MRI or CT examination planned within 72 hours after surgery

Patient and Public Involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Who will take informed consent? {26a}

Patients will be informed verbally and in writing about the study by members of the study team. The information will be given at least one day before the surgical procedure to ensure enough time to consider participation. We emphasize that participation in the study does not impose a significant additional burden on patients as only short questionnaires need to be completed which do not entail any significant risks or unreasonable questions.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Furthermore, patients will be informed and educated in detail about other aspects:

- The intended further use of the non-genetic data for research purposes;
- Their right to refuse or withdraw consent at any time without justification;
- Their right to be informed of the results affecting their health and their right to waive this information;
- The measures taken to protect personal data;
- The possibility of sharing the personal data with third parties for research purposes.
- The collection of patients' consent will take place after the study has been approved by the Ethics Committee.

Interventions

Explanation for the choice of comparators {6b}

The authors hypothesize that the optimal period for postoperative imaging is 36 to 72 hours and therefore decided to include the early time frame (within 36 hours) as an adequate comparator. The authors will also compare the outcomes between the group undergoing postoperative CT and the group undergoing postoperative MRI.

Intervention description {11a}

In general, all patients in our institution receive postoperative imaging within the first 72 hours after a craniotomy for a space-occupying lesion or vascular procedure. The study intervention includes the completion of a questionnaire right before and after the postoperative radiological investigation (Figure 1). Patients are divided in two groups depending on the time interval between end of surgery and radiological investigation: late group (completing the questionnaire 36 to 72 hours after surgery) and early group (completing the questionnaire within 36 hours after surgery). The time intervals to the radiological investigation are assigned by coincidence and the patients are not randomized into any group. The exact time interval until examination depends on various factors, e.g.: capacity of the department of neuroradiology or weekday of surgery (patients operated on Friday are more likely to receive postoperative imaging on Monday; patients operated on Thursday are most likely receive it on Friday) and patient condition (early imaging will more likely be performed in suspected postoperative complications). We decided to use this way of defining the comparators as we are primarily interested in examining potential differences between groups, rather than assessing causality between delayed imaging and stress level.

The questionnaire consists of visual analog scale (VAS) for headache, visual analog scale (VAS) for nausea, and Body Part Discomfort Scale (Figures 2, 3 and 4). At the end of the questionnaire, patients will be asked to answer the following question:

In your opinion, should the MRI and/or CT scan have been performed earlier or later? The possible answers are:

- Yes, earlier;
- Yes, later;
- No, I am satisfied with the timing of the exam.

The authors have chosen these scales because they are validated and simple to understand and register. The completion of each questionnaire will take 5 to 10 minutes, and the burden for each patient is assumed to be low as the questionnaires do not contain any unreasonable questions.

Criteria for discontinuing or modifying allocated interventions {11b}

Although patients might have signed the informed consent situations that do not allow for completion of the questionnaires can occur. Reasons include postoperative complications leading to imaging in intubated patients, emergency imaging in extubated patients, , or the neurosurgeon's decision not to perform postoperative imaging due to case-specific considerations. These patients will be excluded from analysis and the reason for not

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3 completing the questionnaire will be registered.
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6 **Strategies to improve adherence to interventions {11c}**

7 This study is implemented in close and intensive collaboration with nursing staff and
8 supported by residents, medical students and administrative staff. Through this collaboration
9 the study team has managed to create sufficient resources ensuring a high and optimal
10 adherence to the intervention.
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13 **Relevant concomitant care permitted or prohibited during the trial {11d}**

14 None, the interval to radiological investigation will not be delayed due to completion of the
15 questionnaire.
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18 **Provisions for post-trial care {30}**

19 Participants will be informed about the results by an information letter, if interested. The
20 scheduling of future postoperative imaging will be planned based on this study's results.
21
22

23 **Outcomes {12}**

24 The primary endpoint of the study is the difference in subjective stress after craniotomy
25 measured right before and after postoperative MRI or CT imaging with the mentioned
26 instruments. Subjective stress is evaluated as a combination of the scores VAS pain, VAS
27 nausea, and 0.5* Body Part Discomfort score (Figures 2, 3 and 4). A minimum score of 4.5
28 and a maximum score of 42.5 can be achieved.
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32 The secondary endpoints of the study are divided into two groups:
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34 1. Patient specific secondary endpoint:

- 35 • patient interpretation of whether MRI follow-up was performed at the correct interval.
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39 2. Radiology specific secondary endpoints:

- 40 • residual tumor on MRI.
41
42 • contrast enhancement on MRI (postoperative reactive change, not tumor specific).
43
44 • significant post-operative bleeding.
45
46 • Infarction.
47
48 • residual perfusion of the aneurysm or AVM/AVF remnant.
49
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51 **Participant timeline (Figure 1) {13}**

52 Patients are screened on the hospital admission day by the study team and informed consent
53 is taken if inclusion criteria are fulfilled and if no exclusion criteria are met. Questionnaires
54 are completed by patients immediately before and after postoperative MRI or CT imaging.
55 The study is finished for each patient after having completed the post-investigational
56 questionnaire. If either or both questionnaire(s) cannot be completed, the patient's study
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3 participating is finished after the radiological investigation. Radiological findings are
4 assessed and documented in writing by a neuroradiologist according to local guidelines.
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8 **Sample size {14}**

9 A sample measurement of VAS scores in 100 patients with craniotomy for tumour resection
10 in 2019 resulted in a mean score of 1.8 (VAS pain) and 0.8 (VAS nausea). Because there was
11 no baseline data for the Body Part Discomfort score, it was equated to the percentage of VAS
12 pain per patient. This resulted in an average Body Part Discomfort score of 12.3 points. For
13 calculating the total score, the VAS-scores and half of the points from the Body Part
14 Discomfort score are used. The total mean score of all three measurements then becomes 13.6
15 (standard deviation 5.4). To measure an expected change of one third for the separate scores
16 with a power of 80% and a type I error of 5%, a total of 224 patients are required for the
17 study. To correct for any loss to follow-up, we will include 230 patients in this study.
18
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23 **Recruitment {15}**

24 The study team screens all the patients on the admission day based on demographics,
25 diagnosis and planned operation. All adult patients receiving craniotomy for a space
26 occupying lesion or vascular indications are asked to participate in the study.
27
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30 **Data collection and management**

31 **Plans for assessment and collection of outcomes {18a}**

32 Data will be collected from all patients aged 18 to 80 years who receive postoperative MRI or
33 CT follow-up after craniotomy for resection of a cerebral space-occupying lesion (benign and
34 malignant) or vascular procedure using a questionnaire. Radiological findings are assessed
35 and documented in writing by a neuroradiologist according to local guidelines.
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41 The CRF collects the following information and scores:

- 42
43 - Demographic data of patients (sex, age)
44
45 - Localization of craniotomy (side, supra- or infratentorial, lobe and region)
46
47 - Time interval (in hours and postoperative day) between end of surgery and start of MRI or
48 CT scan
49
50 - Indications for post operative imaging as per the surgeon
51
52 - Neuroradiology reports of postoperative imaging examinations
53
54 - Patient related criteria:
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56
 - 57 • Visual analog scale (VAS) for headache (Figure 2).(9)
 - 58 • VAS for nausea (Figure 3).(9)
 - 59 • Body Part Discomfort Scale (Figure 4)(10).

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At the end of the second questionnaire, patients will be asked to answer the following question:

- In your opinion, should the MRI and/or CT scan have been performed earlier or later? The possible answers are:

- Yes, earlier;
- Yes, later;
- No, I am satisfied with the timing of the exam.

The radiological criteria that will be examined are as follows:

- Location of tumor (supra- or infratentorial, left or right)
- Tumor remnant on MRI
- Contrast enhancement on MRI (postoperative reactive change, not tumor-specific)
- Significant postoperative hemorrhage
- Postoperative infarction
- Residual perfusion of the aneurysm or AVM/AVF remnant

Plans to promote participant retention and complete follow-up {18b}

In this study, patients will complete a questionnaire before and after postoperative radiological examination. At the morning rounds, nursing staff is informed about patients who are planned for radiological examination and who are included in the study. When the nursing staff is informed about the exact time for the MRI or CT, the attending nurse (supported by a resident or a medical student if necessary) gives the questionnaire to the patient. The nurse is continuously reminded for this step, thanks to a comment in the digital patient report system (KISIM). Nursing staff and medical staff will monitor the completion of the questionnaires and can support at any time.

Data management {19}

Source data are available as paper questionnaires from patients and as digital documentation in the hospital-wide patient report system (KISIM) for clinical and radiological information. These data are pseudonymized, coded and stored in the form of the coded data in two Microsoft Access tables. One table contains the patient's hospital identification number, date of birth, and study number. The second Microsoft Access table contains all coded study data and patients are identified by study number only. Both tables are protected with passwords

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3 and are stored in a secured folder and are only accessible for study team members. Completed
4 questionnaires are stored in a closed cabinet (available in research office and only accessible
5 to the Project Leader of the study).
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9 **Confidentiality {27}**

10 Personal and medical data will be collected for this study. When data is collected for study
11 purposes, the data is pseudonymized and coded. The coding ensures that all reference data
12 that would reveal the identity of a patient (name, date of birth) is deleted and replaced by a
13 key. The list of keys always remains in the institution/hospital. In the case of a publication,
14 the summarized data cannot be traced back to an individual person. The name of a patient
15 will never appear on the internet or in any publication.
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20 **17. Data storage details**

21 The generation, transfer, storage, and analysis of health data within the scope of this project is
22 carried out in strict compliance with the current legal provisions for data in Swiss Protection
23 and is carried out according to the HRO regulation Art. 5.
24
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26

27 All persons who have access to patient data within the scope of the study are subject to the
28 obligation of confidentiality.
29

30 It is possible that the study will be reviewed by the ethics committee or by the institution that
31 initiated the study. The investigator may have to disclose personal and medical data for such
32 controls. All persons must maintain absolute confidentiality.
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37 **Statistical methods**

38 **Statistical methods for primary and secondary outcomes {20a}**

39 For data analysis, patients are being divided into 2 groups based on predefined time intervals:
40
41

- 42 1. early imaging: within 36 hours postoperatively.
- 43 2. late imaging: between 36 and 72 hours postoperatively.
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48 A second analysis is performed, dividing patients into the following groups:
49

- 50 1. early imaging: on the same day of surgery (day 0) or 1st postoperative day.
- 51 2. late imaging: on the 2nd or 3rd postoperative day.
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56 A third analysis will be performed, dividing the patients based on the radiological
57 examination performed (MRI or CT).
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3 Descriptive data will be investigated for a normal distribution. In case of a normal
4 distribution, results will be presented as means with standard deviations and groups compared
5 by Chi-square tests. If not, the results will be presented as medians with interquartile ranges
6 and results of a non-parametric (Fisher's exact test) will be reported. Results of pre- and post-
7 imaging questionnaires are compared with the paired t-test, or Wilcoxon signed rank test in
8 case of a non-normal distribution of data. The primary outcome is assessed by subtracting the
9 mean subjective stress score before the investigation from the score after the investigation.
10 Crude and adjusted stress score differences are calculated in relation to the predefined time
11 interval groups with logistic regression analysis. Confounders are considered when the
12 change in stress score is >10% in the stratification for the respective parameter. A
13 multivariable regression analysis is performed, adjusting for confounders. A secondary
14 analysis is done by calculating the relative change in stress score before and after the
15 investigation and their corresponding 95% confidence interval (CI), with multivariable
16 regression analysis with confounders as described above.

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23 Secondary endpoints are reported unadjusted with corresponding 95% CI.

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25 A p-value of <0.05 is considered a significant difference. All analyses are done using STATA
26 16.1 or higher (StataCorp LLC, Texas, USA).

27 28 29 **Interim analyses {21b}**

30
31 No interim analyses are planned due to the low risk of the study intervention and an assumed
32 minimal burden to the patients.

33 34 35 36 37 **Methods in analysis to handle protocol non-adherence and any statistical methods to 38 handle missing data {20c}**

39
40 Postoperative complications requiring postoperative imaging in intubated patients unable to
41 complete the questionnaire and emergency imaging in extubated patients with relevant time
42 and personnel limitations are criteria for not performing the questionnaire. Furthermore,
43 questionnaires will not be performed in case the surgeon decides not to perform postoperative
44 imaging. These situations are defined as protocol deviations and these patients will be
45 excluded from analysis.

46
47 If only the data before postoperative imaging (only part of the questionnaire before
48 radiological examination fulfilled) are acquired and post-imaging data are missing, these
49 collected data will only be used in the baseline characteristics and not in the analysis of the
50 primary outcome. However, if the collected data include secondary outcomes, they will be
51 included into the secondary data analysis.

52 53 54 55 56 **Plans to give access to the full protocol, participant level-data and statistical code {31c}**

57
58 We aim to publish the full study protocol in a peer-reviewed medical journal. Full access is
59 granted to the original protocol and participant level-data after consideration with the
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3 corresponding author. The statistical code is written in STATA (StataCorp LLC, Texas,
4 USA) and available upon request.
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7 **Oversight and monitoring**

8
9 No external monitoring is planned due to the low risk of the intervention (questionnaire) and
10 an assumed small burden for study participants. Internal monitoring by the project leader and
11 study coordinator is performed after including the first 10% of patients.
12
13

14 **Adverse event reporting and harms {22}**

15
16 Participation in the study includes only the completion of a questionnaire, in which we do not
17 expect to encounter (serious) adverse events ((S)AE). Nevertheless, if an (S)AE occurs, the
18 project leader and the sponsor will be notified within 24 hours and decide if immediate safety
19 and protective measures have to be taken during the conduct of the research project. The
20 Ethics Committee will be notified of these measures and of the underlying circumstances via
21 BASEC within 7 days.
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26 **Frequency and plans for auditing trial conduct {23}**

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28 The department of neurosurgery of the USZ undergoes a research audit every five years to
29 guarantee high quality of the conducted scientific research. Due to the low risk of the current
30 study, no additional study specific audit is planned.
31
32

33 **Plans for communicating important protocol amendments to relevant parties (e.g. trial 34 participants, ethical committees) {25}**

35
36 Substantial changes to the project set-up, the protocol, and relevant project documents will be
37 submitted to the Ethics Committee for approval according to HRO Art. 18 using the BASEC
38 system. The study team and nursing staff will be informed by oral information and email about
39 important protocol changes.
40
41

42 **Ethics and dissemination {31a}**

43
44 The final decision on the publication of the results will be made by the sponsor (Luca Regli)
45 and the project leader (Menno R. Germans). Authors of the publication are persons who
46 conceived and planned the study or performed parts of the statistical analysis. Unless Luca
47 Regli and Menno R. Germans decide otherwise, Lazar Tosic is the first author and Menno R.
48 Germans is the last author. Joint first or last authorship may be decided if other investigators
49 qualify appropriately by spending a large amount of time and effort on the study. All data
50 belong to Luca Regli and Menno R. Germans, who will decide on authorship, order of
51 authors, journals to be published, and partial results and aspects of the final analysis.
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56 In consultation with Luca Regli and Menno R. Germans, parts of the study results may be
57 analyzed separately by the participating investigators; for these analyses and publications, the
58 first and last authors as well as the order of authorship will be determined by the sponsor,
59 project leader and the principal investigator of the subproject.
60

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5 The institutional review board (Cantonal Ethics Committee Zürich) approved this study on 4th
6 of August 2020 under case number: BASEC 2020-01590, Protocol version: 1.0; Protocol
7 date: 25.06.2020.
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10 11 **Trial status**

12 Patient recruitment started on September 20th 2020. Until February 5th 2022 we had recruited
13 120 participants. With the current inclusion rate, we expect to have the final data in January
14 2023.
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17 18 19 **Abbreviations**

| | | |
|----|--------------|---|
| 20 | | |
| 21 | | |
| 22 | BASEC | Business Administration System for Ethical Committees |
| 23 | | |
| 24 | CRF | Case report form |
| 25 | | |
| 26 | FOPH | Federal Office of Public Health |
| 27 | | |
| 28 | HRA | Human Research Act |
| 29 | | |
| 30 | HRO | Human research ordinance |
| 31 | | |
| 32 | MRI | Magnetic resonance imaging |
| 33 | | |
| 34 | VAS | Visual analogue scale |
| 35 | | |
| 36 | CT | Computed tomography |
| 37 | | |
| 38 | AVM | Arteriovenous malformation |
| 39 | | |
| 40 | AVF | Arteriovenous fistula |
| 41 | | |
| 42 | USZ | University Hospital Zurich |
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47 **Declarations**

48 49 **Authors' contributions**

50 Study concept and initiation: Menno R. Germans, Lazar Tomic and Luca Regli

51 Data collection: Marco Thoma, Stefanos Voglis, Delal Bektas, Anna-Sophie Hofer and Atina
52 Pangalu

53 Data analysis: Lazar Tomic, Menno R. Germans

54 Writing manuscript: Lazar Tomic, Menno R. Germans

55 Critically reviewing manuscript: all authors
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Funding

The project is funded by the Department of Neurosurgery of the University Hospital Zurich.

Availability of data and material

The data is encrypted and entered into Microsoft Access study-specific patient ID, which is password protected and stored on the hospital servers of the University Hospital Zurich. Access to the data for the other colleagues in the department of Neurosurgery of the University Hospital Zurich can only be granted by the project leader and in case of participation in the study team.

Ethics approval and consent to participate

The institutional review board (Kantonale Ethikkommission Zürich) approved this study on 4th of August 2020 under case number: BASEC 2020-01590, Protocol version: 1.0; Protocol date: 25.06.2020.

Consent for publication

All participants gave their written consent for publication (Informed consent version 1.0; informed consent date 14.08.2020).

Competing interests

None to declare

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14 **Figures**

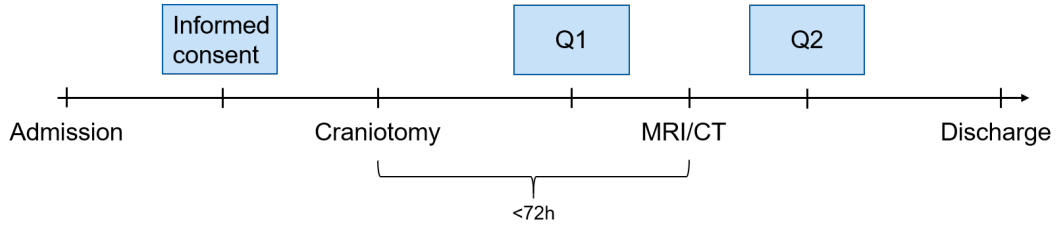
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16 **Figure 1:** Participant timeline ; Q1: pre-imaging questionnaire assessing headache, nausea, and
17 discomfort; Q2: post-imaging questionnaire assessing headache, nausea, discomfort, and
18 timing of imaging
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20 **Figure 2:** Visual analog scale (VAS) for headache
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22 **Figure 3:** Visual analog scale (VAS) for nausea
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24 **Figure 4:** Body Part Discomfort Scale
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For peer review only

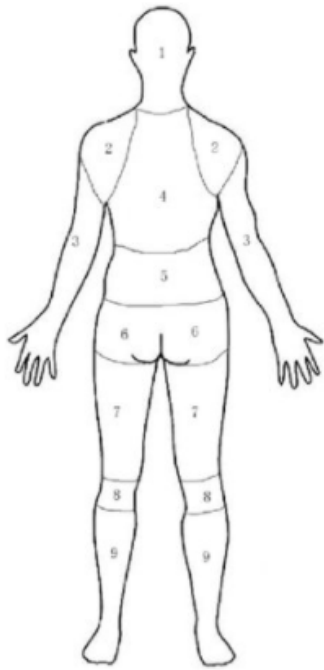
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| nausea | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | I can imagine |

For peer review only



1 Not uncomfortable 4 Very uncomfortable
2 Barely uncomfortable 5 Extremely uncomfortable
3 Quite uncomfortable

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| 1 Head and neck | <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 |
| 2 Shoulder | <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 |
| 3 Arm | <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 |
| 4 Middle back | <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 |
| 5 Low back | <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 |
| 6 Buttock | <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 |
| 7 Thigh | <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 |
| 8 Knee | <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 |
| 9 Leg and foot | <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 |

Peer review only

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BMJ Open

Evaluation of patient STress level caused by radiological Investigations in early Postoperative phase After CRANIOTomy (IPAST-CRANIO): protocol of a Swiss prospective cohort study

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|---------------------------------|--|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2022-061452.R3 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 23-Jun-2022 |
| Complete List of Authors: | Tosic, Lazar; UniversitätsSpital Zürich, Neurosurgery Thoma, Marco; Department of Neurosurgery, University Hospital Zurich, Switzerland Voglis, Stefanos; University Hospital Zurich, Neurosurgery Hofer, Anna Sophie; Department of Neurosurgery, University Hospital Zurich, Switzerland Bektas, Delal; Department of Neurosurgery, University Hospital Zurich, Switzerland Pangalu, Athina; Department of Neurosurgery, University Hospital Zurich, Switzerland Regli, Luca; University Hospital Zurich, Neurosurgery Germans, Menno; University Hospital Zurich, Neurosurgery |
| Primary Subject Heading: | Surgery |
| Secondary Subject Heading: | Patient-centred medicine, Qualitative research, Radiology and imaging |
| Keywords: | Computed tomography < RADIOLOGY & IMAGING, NEUROSURGERY, Magnetic resonance imaging < RADIOLOGY & IMAGING |
| | |

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Manuscripts

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4 **Evaluation of patient STress level caused by radiological Investigations in early**
5 **Postoperative phase After CRANIOTomy (IPAST-CRANIO): protocol of a Swiss**
6 **prospective cohort study**
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Abstract

Introduction:

Postoperative imaging after neurosurgical interventions is usually performed in the first 72 hours after surgery to provide an accurate assessment of postoperative resection status. Patient frequently report that early postoperative examination after craniotomy for tumor and vascular procedures is associated with distress, exertion, nausea, and pain. Delayed postoperative imaging (between 36 and 72 hours postoperatively) may have an advantage regarding psychological and physical stress compared to early imaging. The goal of this study is to evaluate and determine the optimal time frame for postoperative imaging with MRI and CT in terms of medical and neuroradiological implications and patient's subjective stress level.

Methods and Analysis

Data will be prospectively collected from all patients aged 18 to 80 years who receive postoperative MRI or CT imaging following a craniotomy for resection of a cerebral tumor (benign and malignant) or vascular surgery. Participants have to complete questionnaires containing visual analogue scores for headache and nausea (VAS), Body Part Discomfort score and a single question addressing subjective preference of timing of postoperative imaging after craniotomy. The primary endpoint of the study is the difference in subjective stress due to imaging studies after craniotomy, measured just before and after postoperative MRI or CT with the above mentioned instruments. Subjective stress is defined as a combination of the scores VAS pain, VAS nausea, and $0.5 \times$ Body Part Discomfort score.

This study determines whether proper timing of postoperative imaging can improve patient satisfaction and reduce pain, stress and discomfort caused by postoperative imaging. Factors causing additional postoperative stress are likely responsible for delayed recovery of neurosurgical patients.

Ethics and Dissemination

The institutional review board (Kantonale Ethikkommission Zürich) approved this study on 4 August 2020 under case number BASEC 2020-01590. The authors are planning to publish the data of this study in a peer-reviewed paper. After database closure, the data will be exported to the local data repository (Zurich Open Repository and Archive) of the University of Zurich. The sponsor (Luca Regli) and the project leader (Menno R. Germans) will make the final decision on the publication of the results. The data that support the findings of this study are available on request from the corresponding author Lazar Tomic. The data are not publicly available due to privacy/ethical restrictions.

Registration

This trial has also been registered in Clinical Trials under ClinicalTrials.gov ID: NCT05112575.

Strengths and limitations of this study

The main strengths:

- prospective
- patient-oriented study design
- large number of participants with predefined sample size calculation
-

The main limitations:

- single centre study
- no randomisation of participants

Keywords

Magnetic resonance imaging – computed tomography - craniotomy – postoperative imaging

Administrative information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers.

The order of the items has been modified to group similar items (see <http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/>)

| | |
|---------------------------------|--|
| Title (1) | Evaluation of patient stress level caused by radiological investigations in early postoperative phase after craniotomy (IPAST-CRANIO) |
| Trial registration {2a and 2b}. | <p>The institutional review board (Kantonale Ethikkommission Zürich) approved this study on 4 August 2020 under case number: BASEC 2020-01590.</p> <p>This trial has also been registered in Clinical Trials under ClinicalTrials.gov ID: NCT05112575.</p> |
| Protocol version {3} | 1.0, 25.06.2020 |
| Funding {4} | This research is financed by the Department of Neurosurgery, University Hospital Zurich, Switzerland. |

| | |
|---|--|
| Author details {5a} | Lazar Tosic, MD Marco Thoma, cand. MScN Stefanos Voglis, MD Anna-Sophie Hofer, MD, PhD A. Pangalu, MD Luca Regli, MD Menno R. Germans, MD, PhD |
| Name and contact information for the trial sponsor {5b} | Prof. Dr. Luca Regli E-Mail: luca.regli@usz.ch Tel.: +4144255992 |
| Role of sponsor {5c} | Design; management, analysis and interpretation of data; critically reviewing the manuscript; and the decision to submit the report for publication. |

Introduction {6a}

Magnetic resonance imaging (MRI) after neurosurgical resection of a cerebral tumor is usually performed in the first 72 hours after surgery. (1-5) Accurate assessment of early postoperative resection status of brain tumors is mandatory for further treatment planning, e.g., delineation of the radiation field during radiotherapy, or reoperation for significant residual tumor. (6) Various MRI-sequences provide information on tumor size and location, as well as additional insight into secondary phenomena such as edema, hemorrhage, infarct, necrosis, and signs of increased intracranial pressure. (1, 3, 6, 7) The 72 hours time window is crucial for accurate assessment of resection status and is additionally used for quality control of neurosurgical procedures. (8) Postoperative MRI performed later than 72 hours after surgery can lead to false positive contrast enhancement due to absorption of contrast in the surgical area which can complicate the assessment of resection status. (1, 7) Postsurgical repair mechanisms at the resection site resulting from hypervascularization and disruption of the blood-brain barrier are probably responsible for this delayed enhancement. (8)

The potential advantages of early imaging (within 36 hours after surgery) are better radiological assessment of the surgical site and earlier diagnosis of postoperative complications, such as infarcts, postoperative bleeding or edema. This may help improve the postoperative management of patients with complications. Moreover, earlier information about the outcome of surgery could also lead to psychological relief for patients in the early

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3 postoperative period. Disadvantages of early postoperative examinations after craniotomy are
4 frequently reported by patients and include distress, exertion, nausea, and pain during and
5 after the examination. As such, psychological and physical patient stress could be a potential
6 disadvantage of early (within 36 hours after surgery) MRI examination. An alternative image
7 modality is computed tomography (CT), which may be less stressful for patients as it takes
8 only 5 to 10 minutes to complete the scan and patients do not have to lie in a narrow scanner
9 as for MRI examinations. However, with this modality the postoperative resection status
10 cannot be reliably assessed. To our knowledge, no previous literature has been published
11 which addressed stress factors during postoperative imaging. To our opinion, a more patient-
12 centered design of the early postoperative course including timing of postoperative imaging
13 studies requires the investigation of patient stress levels associated with postoperative
14 imaging performed at different time intervals from surgery. With the optimization of the
15 postoperative time window for MRI and CT examinations we aim to improve psychological
16 and physical patient stress, which may have a positive influence on early recovery.
17 Additionally, establishing an optimal time window for postoperative MRI imaging will help
18 in scheduling the examination before the elective surgical treatment. This will have a positive
19 impact on preparing patients, radiology employees, nurses and physicians for a smooth and
20 easy transport to and from the MRI examination.
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29 **Objectives {6a}**

30 The goal of this study is to assess whether early imaging with MRI (within 36 hours) after
31 craniotomy has a different impact on patient stress compared to delayed imaging (between 36
32 and 72 hours). Secondly, we aim to assess whether there is a difference in patient stress level
33 between postoperative MRI and CT performed within 72 hours postoperatively.
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36 The authors hypothesize that delayed MRI imaging after craniotomy is more comfortable for
37 patients without having negative implications on the validity and reliability of radiological
38 assessments compared to imaging performed within 36 hours. Secondly, we hypothesize that
39 postoperative MRI is more stressful for patients than postoperative CT.
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44 **Trial design {8}**

45 The IPAST-CRANIO study (Evaluation of patient Stress level caused by radiological
46 Investigations in early Postoperative phase After CRANIotomy) is a patient-oriented,
47 prospective, exploratory cohort study.
48
49

50 **Methods: Participants, interventions and outcomes**

51 **Study setting {9}**

52 Data will be collected from patients between 18 and 80 years old who receive MRI or CT
53 follow-up studies after craniotomy for resection of a space occupying lesion (benign or
54 malignant) or vascular procedure at the Department of Neurosurgery at the University
55 Hospital Zurich.
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59 **Eligibility criteria {10}**

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- Written consent of the patient
- Age between 18 and 80 years
- Planned supra- or infratentorial (partial) resection of space occupying lesion (benign or malignant) or vascular neurosurgical procedure (clipping of an aneurysm, resection of an arteriovenous malformation/fistula, resection of cavernoma)
- Planned MRI or CT follow-up within 72 hours after surgery

The presence of any of the following exclusion criteria will lead to exclusion of the participant:

- No informed consent
- Surgery involving only one burr hole (e.g. biopsy) instead of craniotomy
- Not able to fill out the questionnaires due to cognitive impairment or aphasia
- Not German or English speaking
- Contraindication for MRI/CT examination
- No postoperative MRI or CT examination planned within 72 hours after surgery

Patient and Public Involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Who will take informed consent? {26a}

Patients will be informed verbally and in writing about the study by members of the study team. The information will be given at least one day before the surgical procedure to ensure enough time to consider participation. We emphasize that participation in the study does not impose a significant additional burden on patients as only short questionnaires need to be completed which do not entail any significant risks or unreasonable questions.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Furthermore, patients will be informed and educated in detail about other aspects:

- The intended further use of the non-genetic data for research purposes;
- Their right to refuse or withdraw consent at any time without justification;
- Their right to be informed of the results affecting their health and their right to waive this information;
- The measures taken to protect personal data;
- The possibility of sharing the personal data with third parties for research purposes.

- The collection of patients' consent will take place after the study has been approved by the Ethics Committee.

Interventions

Explanation for the choice of comparators {6b}

The authors hypothesize that the optimal period for postoperative imaging is 36 to 72 hours and therefore decided to include the early time frame (within 36 hours) as an adequate comparator. The authors will also compare the outcomes between the group undergoing postoperative CT and the group undergoing postoperative MRI.

Intervention description {11a}

In general, all patients in our institution receive postoperative imaging within the first 72 hours after a craniotomy for a space-occupying lesion or vascular procedure. The study intervention includes the completion of a questionnaire right before and after the postoperative radiological investigation (Figure 1). Patients are divided in two groups depending on the time interval between end of surgery and radiological investigation: late group (completing the questionnaire 36 to 72 hours after surgery) and early group (completing the questionnaire within 36 hours after surgery). The time intervals to the radiological investigation are assigned by coincidence and the patients are not randomized into any group. The exact time interval until examination depends on various factors, e.g.: capacity of the department of neuroradiology or weekday of surgery (patients operated on Friday are more likely to receive postoperative imaging on Monday; patients operated on Thursday are most likely receive it on Friday) and patient condition (early imaging will more likely be performed in suspected postoperative complications). We decided to use this way of defining the comparators as we are primarily interested in examining potential differences between groups, rather than assessing causality between delayed imaging and stress level.

The questionnaire consists of visual analog scale (VAS) for headache, visual analog scale (VAS) for nausea, and Body Part Discomfort Scale (Figures 2, 3 and 4). At the end of the questionnaire, patients will be asked to answer the following question:

In your opinion, should the MRI and/or CT scan have been performed earlier or later? The possible answers are:

- Yes, earlier;
- Yes, later;
- No, I am satisfied with the timing of the exam.

The authors have chosen these scales because they are validated and simple to understand and register. The completion of each questionnaire will take 5 to 10 minutes, and the burden for each patient is assumed to be low as the questionnaires do not contain any unreasonable questions.

Criteria for discontinuing or modifying allocated interventions {11b}

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3 Although patients might have signed the informed consent situations that do not allow for
4 completion of the questionnaires can occur. Reasons include postoperative complications
5 leading to imaging in intubated patients, emergency imaging in extubated patients, , or the
6 neurosurgeon's decision not to perform postoperative imaging due to case-specific
7 considerations. These patients will be excluded from analysis and the reason for not
8 completing the questionnaire will be registered.
9
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11 **Strategies to improve adherence to interventions {11c}**

12 This study is implemented in close and intensive collaboration with nursing staff and
13 supported by residents, medical students and administrative staff. Through this collaboration
14 the study team has managed to create sufficient resources ensuring a high and optimal
15 adherence to the intervention.
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19 **Relevant concomitant care permitted or prohibited during the trial {11d}**

20 None, the interval to radiological investigation will not be delayed due to completion of the
21 questionnaire.
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25 **Provisions for post-trial care {30}**

26 Participants will be informed about the results by an information letter, if interested. The
27 scheduling of future postoperative imaging will be planned based on this study's results.
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30 **Outcomes {12}**

31 The primary endpoint of the study is the difference in subjective stress after craniotomy
32 measured right before and after postoperative MRI or CT imaging with the mentioned
33 instruments. Subjective stress is evaluated as a combination of the scores VAS pain, VAS
34 nausea, and 0.5* Body Part Discomfort score (Figures 2, 3 and 4). A minimum score of 4.5
35 and a maximum score of 42.5 can be achieved.
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39 The secondary endpoints of the study are divided into two groups:
40

41 1. Patient specific secondary endpoint:

- 42 • patient interpretation of whether MRI follow-up was performed at the correct interval.

43 2. Radiology specific secondary endpoints:

- 44 • residual tumor on MRI.
- 45 • contrast enhancement on MRI (postoperative reactive change, not tumor specific).
- 46 • significant post-operative bleeding.
- 47 • Infarction.
- 48 • residual perfusion of the aneurysm or AVM/AVF remnant.

49 **Participant timeline (Figure 1) {13}**

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3 Patients are screened on the hospital admission day by the study team and informed consent
4 is taken if inclusion criteria are fulfilled and if no exclusion criteria are met. Questionnaires
5 are completed by patients immediately before and after postoperative MRI or CT imaging.
6 The study is finished for each patient after having completed the post-investigational
7 questionnaire. If either or both questionnaire(s) cannot be completed, the patient's study
8 participating is finished after the radiological investigation. Radiological findings are
9 assessed and documented in writing by a neuroradiologist according to local guidelines.
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15 **Sample size {14}**

16 A sample measurement of VAS scores in 100 patients with craniotomy for tumour resection
17 in 2019 resulted in a mean score of 1.8 (VAS pain) and 0.8 (VAS nausea). Because there was
18 no baseline data for the Body Part Discomfort score, it was equated to the percentage of VAS
19 pain per patient. This resulted in an average Body Part Discomfort score of 12.3 points. For
20 calculating the total score, the VAS-scores and half of the points from the Body Part
21 Discomfort score are used. The total mean score of all three measurements then becomes 13.6
22 (standard deviation 5.4). To measure an expected change of one third for the separate scores
23 with a power of 80% and a type I error of 5%, a total of 224 patients are required for the
24 study. To correct for any loss to follow-up, we will include 230 patients in this study.
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30 **Recruitment {15}**

31 The study team screens all the patients on the admission day based on demographics,
32 diagnosis and planned operation. All adult patients receiving craniotomy for a space
33 occupying lesion or vascular indications are asked to participate in the study.
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37 **Data collection and management**

38 **Plans for assessment and collection of outcomes {18a}**

39 Data will be collected from all patients aged 18 to 80 years who receive postoperative MRI or
40 CT follow-up after craniotomy for resection of a cerebral space-occupying lesion (benign and
41 malignant) or vascular procedure using a questionnaire. Radiological findings are assessed
42 and documented in writing by a neuroradiologist according to local guidelines.
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48 The CRF collects the following information and scores:

- 49 - Demographic data of patients (sex, age)
- 50 - Localization of craniotomy (side, supra- or infratentorial, lobe and region)
- 51 - Time interval (in hours and postoperative day) between end of surgery and start of MRI or
52 CT scan
- 53 - Indications for post operative imaging as per the surgeon
- 54 - Neuroradiology reports of postoperative imaging examinations
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3 - Patient related criteria:

- 4 • Visual analog scale (VAS) for headache (Figure 2).(9)
- 5 • VAS for nausea (Figure 3).(9)
- 6 • Body Part Discomfort Scale (Figure 4)(10).

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11 At the end of the second questionnaire, patients will be asked to answer the following
12 question:

13
14 - In your opinion, should the MRI and/or CT scan have been performed earlier or later? The
15 possible answers are:

- 16 ○ Yes, earlier;
- 17 ○ Yes, later;
- 18 ○ No, I am satisfied with the timing of the exam.

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23 The radiological criteria that will be examined are as follows:

- 24 - Location of tumor (supra- or infratentorial, left or right)
- 25 - Tumor remnant on MRI
- 26 - Contrast enhancement on MRI (postoperative reactive change, not tumor-specific)
- 27 - Significant postoperative hemorrhage
- 28 - Postoperative infarction
- 29 - Residual perfusion of the aneurysm or AVM/AVF remnant

30 31 32 33 34 35 36 37 38 39 **Plans to promote participant retention and complete follow-up {18b}**

40 In this study, patients will complete a questionnaire before and after postoperative
41 radiological examination. At the morning rounds, nursing staff is informed about patients
42 who are planned for radiological examination and who are included in the study. When the
43 nursing staff is informed about the exact time for the MRI or CT, the attending nurse
44 (supported by a resident or a medical student if necessary) gives the questionnaire to the
45 patient. The nurse is continuously reminded for this step, thanks to a comment in the digital
46 patient report system (KISIM). Nursing staff and medical staff will monitor the completion of
47 the questionnaires and can support at any time.

48 49 50 51 52 53 **Data management {19}**

54 Source data are available as paper questionnaires from patients and as digital documentation
55 in the hospital-wide patient report system (KISIM) for clinical and radiological information.
56 These data are pseudonymized, coded and stored in the form of the coded data in two
57 Microsoft Access tables. One table contains the patient's hospital identification number, date
58 of birth, and study number. The second Microsoft Access table contains all coded study data
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3 and patients are identified by study number only. Both tables are protected with passwords
4 and are stored in a secured folder and are only accessible for study team members. Completed
5 questionnaires are stored in a closed cabinet (available in research office and only accessible
6 to the Project Leader of the study).
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10 11 12 **Confidentiality {27}**

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14 Personal and medical data will be collected for this study. When data is collected for study
15 purposes, the data is pseudonymized and coded. The coding ensures that all reference data
16 that would reveal the identity of a patient (name, date of birth) is deleted and replaced by a
17 key. The list of keys always remains in the institution/hospital. In the case of a publication,
18 the summarized data cannot be traced back to an individual person. The name of a patient
19 will never appear on the internet or in any publication.
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23 24 25 **17. Data storage details**

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27 The generation, transfer, storage, and analysis of health data within the scope of this project is
28 carried out in strict compliance with the current legal provisions for data in Swiss Protection
29 and is carried out according to the HRO regulation Art. 5.
30
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32 All persons who have access to patient data within the scope of the study are subject to the
33 obligation of confidentiality.
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35 It is possible that the study will be reviewed by the ethics committee or by the institution that
36 initiated the study. The investigator may have to disclose personal and medical data for such
37 controls. All persons must maintain absolute confidentiality.
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41 42 **Statistical methods**

43 **Statistical methods for primary and secondary outcomes {20a}**

44 For data analysis, patients are being divided into 2 groups based on predefined time intervals:
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46

- 47 1. early imaging: within 36 hours postoperatively.
 - 48 2. late imaging: between 36 and 72 hours postoperatively.
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52 A second analysis is performed, dividing patients into the following groups:
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- 54 1. early imaging: on the same day of surgery (day 0) or 1st postoperative day.
 - 55 2. late imaging: on the 2nd or 3rd postoperative day.
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3 A third analysis will be performed, dividing the patients based on the radiological
4 examination performed (MRI or CT).
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6 Descriptive data will be investigated for a normal distribution. In case of a normal
7 distribution, results will be presented as means with standard deviations and groups compared
8 by Chi-square tests. If not, the results will be presented as medians with interquartile ranges
9 and results of a non-parametric (Fisher's exact test) will be reported. Results of pre- and post-
10 imaging questionnaires are compared with the paired t-test, or Wilcoxon signed rank test in
11 case of a non-normal distribution of data. The primary outcome is assessed by subtracting the
12 mean subjective stress score before the investigation from the score after the investigation.
13 Crude and adjusted stress score differences are calculated in relation to the predefined time
14 interval groups with logistic regression analysis. Confounders are considered when the
15 change in stress score is >10% in the stratification for the respective parameter. A
16 multivariable regression analysis is performed, adjusting for confounders. A secondary
17 analysis is done by calculating the relative change in stress score before and after the
18 investigation and their corresponding 95% confidence interval (CI), with multivariable
19 regression analysis with confounders as described above.
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25 Secondary endpoints are reported unadjusted with corresponding 95% CI.
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27 A p-value of <0.05 is considered a significant difference. All analyses are done using STATA
28 16.1 or higher (StataCorp LLC, Texas, USA).
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33 **Interim analyses {21b}**

34 No interim analyses are planned due to the low risk of the study intervention and an assumed
35 minimal burden to the patients.
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40 **Methods in analysis to handle protocol non-adherence and any statistical methods to** 41 **handle missing data {20c}**

42 Postoperative complications requiring postoperative imaging in intubated patients unable to
43 complete the questionnaire and emergency imaging in extubated patients with relevant time
44 and personnel limitations are criteria for not performing the questionnaire. Furthermore,
45 questionnaires will not be performed in case the surgeon decides not to perform postoperative
46 imaging. These situations are defined as protocol deviations and these patients will be
47 excluded from analysis.
48
49

50 If only the data before postoperative imaging (only part of the questionnaire before
51 radiological examination fulfilled) are acquired and post-imaging data are missing, these
52 collected data will only be used in the baseline characteristics and not in the analysis of the
53 primary outcome. However, if the collected data include secondary outcomes, they will be
54 included into the secondary data analysis.
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59 **Plans to give access to the full protocol, participant level-data and statistical code {31c}**

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3 We aim to publish the full study protocol in a peer-reviewed medical journal. Full access is
4 granted to the original protocol and participant level-data after consideration with the
5 corresponding author. The statistical code is written in STATA (StataCorp LLC, Texas,
6 USA) and available upon request.
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12 **Oversight and monitoring**

13 No external monitoring is planned due to the low risk of the intervention (questionnaire) and
14 an assumed small burden for study participants. Internal monitoring by the project leader and
15 study coordinator is performed after including the first 10% of patients.
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20 **Adverse event reporting and harms {22}**

21 Participation in the study includes only the completion of a questionnaire, in which we do not
22 expect to encounter (serious) adverse events ((S)AE). Nevertheless, if an (S)AE occurs, the
23 project leader and the sponsor will be notified within 24 hours and decide if immediate safety
24 and protective measures have to be taken during the conduct of the research project. The
25 Ethics Committee will be notified of these measures and of the underlying circumstances via
26 BASEC within 7 days.
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31 **Frequency and plans for auditing trial conduct {23}**

32 The department of neurosurgery of the USZ undergoes a research audit every five years to
33 guarantee high quality of the conducted scientific research. Due to the low risk of the current
34 study, no additional study specific audit is planned.
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40 **Plans for communicating important protocol amendments to relevant parties (e.g. trial 41 participants, ethical committees) {25}**

42 Substantial changes to the project set-up, the protocol, and relevant project documents will be
43 submitted to the Ethics Committee for approval according to HRO Art. 18 using the BASEC
44 system. The study team and nursing staff will be informed by oral information and email about
45 important protocol changes.
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50 **Ethics and dissemination {31a}**

51 The final decision on the publication of the results will be made by the sponsor (Luca Regli)
52 and the project leader (Menno R. Germans). The authors are planning to publish the data of
53 this study in a peer-reviewed paper. After database closure, the data will be exported to the
54 local data repository (Zurich Open Repository and Archive) of the University of Zurich.
55 Authors of the publication are persons who conceived and planned the study or performed
56 parts of the statistical analysis. Unless Luca Regli and Menno R. Germans decide otherwise,
57 Lazar Tomic is the first author and Menno R. Germans is the last author. Joint first or last
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3 authorship may be decided if other investigators qualify appropriately by spending a large
4 amount of time and effort on the study. All data belong to Luca Regli and Menno R.
5 Germans, who will decide on authorship, order of authors, journals to be published, and
6 partial results and aspects of the final analysis.
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10 In consultation with Luca Regli and Menno R. Germans, parts of the study results may be
11 analyzed separately by the participating investigators; for these analyses and publications, the
12 first and last authors as well as the order of authorship will be determined by the sponsor,
13 project leader and the principal investigator of the subproject.
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17 The institutional review board (Cantonal Ethics Committee Zürich) approved this study on 4th
18 of August 2020 under case number: BASEC 2020-01590, Protocol version: 1.0; Protocol
19 date: 25.06.2020.
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49 1976;19(2):175-82.
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53

54 **Declarations**

55 **Authors' contributions**

56
57
58 Study concept and initiation: Menno R. Germans, Lazar Tomic and Luca Regli
59
60

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3 Data collection: Marco Thoma, Stefanos Voglis, Delal Bektas, Anna-Sophie Hofer and Atina
4 Pangalu

5
6 Data analysis: Lazar Tomic, Menno R. Germans

7 Writing manuscript: Lazar Tomic, Menno R. Germans

8 Critically reviewing manuscript: all authors
9

10 11 **Funding**

12 The project is funded by the Department of Neurosurgery of the University Hospital Zurich.
13
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15 **Competing interests**

16 None to declare
17
18

19 **Trial status**

20 Patient recruitment started on September 20th 2020. Until February 5th 2022 we had recruited
21 120 participants. With the current inclusion rate, we expect to have the final data in January
22 2023.
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25 **Abbreviations**

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29 **BASEC** Business Administration System for Ethical Committees

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31 **CRF** Case report form

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33 **FOPH** Federal Office of Public Health

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35 **HRA** Human Research Act

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37 **HRO** Human research ordinance

38
39 **MRI** Magnetic resonance imaging

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41 **VAS** Visual analogue scale

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43 **CT** Computed tomography

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45 **AVM** Arteriovenous malformation

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47 **AVF** Arteriovenous fistula

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49 **USZ** University Hospital Zurich
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51 52 **Availability of data and material**

53 The data is encrypted and entered into Microsoft Access study-specific patient ID, which is
54 password protected and stored on the hospital servers of the University Hospital Zurich.
55

56 Access to the data for the other colleagues in the department of Neurosurgery of the
57 University Hospital Zurich can only be granted by the project leader and in case of
58 participation in the study team. After database closure, the data will be exported to the local
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3 data repository (Zurich Open Repository and Archive) of the University of Zurich.
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7 **Ethics approval and consent to participate**

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9 The institutional review board (Kantonale Ethikkommission Zürich) approved this study on
10 4th of August 2020 under case number: BASEC 2020-01590, Protocol version: 1.0; Protocol
11 date: 25.06.2020.
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14 **Consent for publication**

15 All participants gave their written consent for publication (Informed consent version 1.0;
16 informed consent date 14.08.2020).
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20 **Figures**

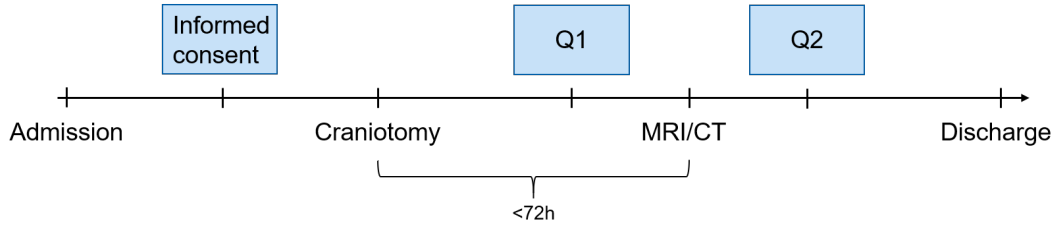
21
22 **Figure 1:** Participant timeline ; Q1: pre-imaging questionnaire assessing headache, nausea, and
23 discomfort; Q2: post-imaging questionnaire assessing headache, nausea, discomfort, and
24 timing of imaging
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28 **Figure 2:** Visual analog scale (VAS) for headache
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30 **Figure 3:** Visual analog scale (VAS) for nausea
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32 **Figure 4:** Body Part Discomfort Scale
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For peer review only

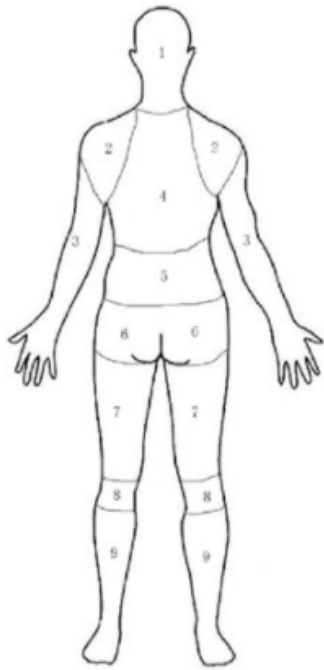
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4 **no** 0 1 2 3 4 5 6 7 8 9 10 **strongest** headache
5 headache I can imagine
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| nausea | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | I can imagine |

For peer review only



1 Not uncomfortable 4 Very uncomfortable
2 Barely uncomfortable 5 Extremely uncomfortable
3 Quite uncomfortable

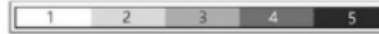
1 Head and neck



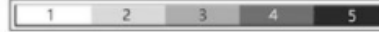
2 Shoulder



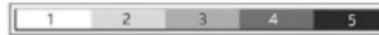
3 Arm



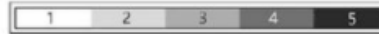
4 Middle back



5 Low back



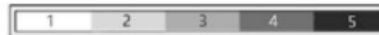
6 Buttock



7 Thigh



8 Knee



9 Leg and foot



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BMJ Open

Evaluation of patient STress level caused by radiological Investigations in early Postoperative phase After CRANIOTomy (IPAST-CRANIO): protocol of a Swiss prospective cohort study

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| Date Submitted by the Author: | 10-Aug-2022 |
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| Primary Subject Heading: | Surgery |
| Secondary Subject Heading: | Patient-centred medicine, Qualitative research, Radiology and imaging |
| Keywords: | Computed tomography < RADIOLOGY & IMAGING, NEUROSURGERY, Magnetic resonance imaging < RADIOLOGY & IMAGING |
| | |

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Manuscripts

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4 **Evaluation of patient STress level caused by radiological Investigations in early**
5 **Postoperative phase After CRANIOTomy (IPAST-CRANIO): protocol of a Swiss**
6 **prospective cohort study**
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11 Lazar Tomic^{1,2}, MD; Marco Thoma¹, cand. MScN; Stefanos Voglis^{1,2}, MD; Anna-Sophie
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Abstract

Introduction:

Postoperative imaging after neurosurgical interventions is usually performed in the first 72 hours after surgery to provide an accurate assessment of postoperative resection status. Patient frequently report that early postoperative examination after craniotomy for tumor and vascular procedures is associated with distress, exertion, nausea, and pain. Delayed postoperative imaging (between 36 and 72 hours postoperatively) may have an advantage regarding psychological and physical stress compared to early imaging. The goal of this study is to evaluate and determine the optimal time frame for postoperative imaging with MRI and CT in terms of medical and neuroradiological implications and patient's subjective stress level.

Methods and Analysis

Data will be prospectively collected from all patients aged 18 to 80 years who receive postoperative MRI or CT imaging following a craniotomy for resection of a cerebral tumor (benign and malignant) or vascular surgery. Participants have to complete questionnaires containing visual analogue scores for headache and nausea (VAS), Body Part Discomfort score and a single question addressing subjective preference of timing of postoperative imaging after craniotomy. The primary endpoint of the study is the difference in subjective stress due to imaging studies after craniotomy, measured just before and after postoperative MRI or CT with the above mentioned instruments. Subjective stress is defined as a combination of the scores VAS pain, VAS nausea, and $0.5 \times$ Body Part Discomfort score.

This study determines whether proper timing of postoperative imaging can improve patient satisfaction and reduce pain, stress and discomfort caused by postoperative imaging. Factors causing additional postoperative stress are likely responsible for delayed recovery of neurosurgical patients.

Ethics and Dissemination

The institutional review board (Kantonale Ethikkommission Zürich) approved this study on 4 August 2020 under case number BASEC 2020-01590. The authors are planning to publish the data of this study in a peer-reviewed paper. After database closure, the data will be exported to the local data repository (Zurich Open Repository and Archive) of the University of Zurich. The sponsor (Luca Regli) and the project leader (Menno R. Germans) will make the final decision on the publication of the results. The data that support the findings of this study are available on request from the corresponding author Lazar Tomic. The data are not publicly available due to privacy/ethical restrictions.

Registration

This trial has also been registered in Clinical Trials under ClinicalTrials.gov ID: NCT05112575.

Strengths and limitations of this study

The main strengths:

- prospective
- patient-oriented study design
- large number of participants with predefined sample size calculation
-

The main limitations:

- single centre study
- no randomisation of participants

Keywords

Magnetic resonance imaging – computed tomography - craniotomy – postoperative imaging

| | |
|---------------------------------|--|
| Title (1) | Evaluation of patient stress level caused by radiological investigations in early postoperative phase after craniotomy (IPAST-CRANIO) |
| Trial registration {2a and 2b}. | <p>The institutional review board (Kantonale Ethikkommission Zürich) approved this study on 4 August 2020 under case number: BASEC 2020-01590.</p> <p>This trial has also been registered in Clinical Trials under ClinicalTrials.gov ID: NCT05112575.</p> |
| Protocol version {3} | 1.0, 25.06.2020 |
| Funding {4} | This research is financed by the Department of Neurosurgery, University Hospital Zurich, Switzerland. |
| Author details {5a} | <p>Lazar Tomic, MD</p> <p>Marco Thoma, cand. MScN</p> <p>Stefanos Voglis, MD</p> <p>Anna-Sophie Hofer, MD, PhD</p> |

| | |
|---|--|
| | A. Pangalu, MD Luca Regli, MD Menno R. Germans, MD, PhD |
| Name and contact information for the trial sponsor {5b} | Prof. Dr. Luca Regli E-Mail: luca.regli@usz.ch Tel.: +4144255992 |
| Role of sponsor {5c} | Design; management, analysis and interpretation of data; critically reviewing the manuscript; and the decision to submit the report for publication. |

Introduction {6a}

Magnetic resonance imaging (MRI) after neurosurgical resection of a cerebral tumor is usually performed in the first 72 hours after surgery. (1-5) Accurate assessment of early postoperative resection status of brain tumors is mandatory for further treatment planning, e.g., delineation of the radiation field during radiotherapy, or reoperation for significant residual tumor. (6) Various MRI-sequences provide information on tumor size and location, as well as additional insight into secondary phenomena such as edema, hemorrhage, infarct, necrosis, and signs of increased intracranial pressure. (1, 3, 6, 7) The 72 hours time window is crucial for accurate assessment of resection status and is additionally used for quality control of neurosurgical procedures. (8) Postoperative MRI performed later than 72 hours after surgery can lead to false positive contrast enhancement due to absorption of contrast in the surgical area which can complicate the assessment of resection status. (1, 7) Postsurgical repair mechanisms at the resection site resulting from hypervascularization and disruption of the blood-brain barrier are probably responsible for this delayed enhancement. (8)

The potential advantages of early imaging (within 36 hours after surgery) are better radiological assessment of the surgical site and earlier diagnosis of postoperative complications, such as infarcts, postoperative bleeding or edema. This may help improve the postoperative management of patients with complications. Moreover, earlier information about the outcome of surgery could also lead to psychological relief for patients in the early postoperative period. Disadvantages of early postoperative examinations after craniotomy are frequently reported by patients and include distress, exertion, nausea, and pain during and after the examination. As such, psychological and physical patient stress could be a potential disadvantage of early (within 36 hours after surgery) MRI examination. An alternative image modality is computed tomography (CT), which may be less stressful for patients as it takes

only 5 to 10 minutes to complete the scan and patients do not have to lie in a narrow scanner as for MRI examinations. However, with this modality the postoperative resection status cannot be reliably assessed. To our knowledge, no previous literature has been published which addressed stress factors during postoperative imaging. To our opinion, a more patient-centered design of the early postoperative course including timing of postoperative imaging studies requires the investigation of patient stress levels associated with postoperative imaging performed at different time intervals from surgery. With the optimization of the postoperative time window for MRI and CT examinations we aim to improve psychological and physical patient stress, which may have a positive influence on early recovery. Additionally, establishing an optimal time window for postoperative MRI imaging will help in scheduling the examination before the elective surgical treatment. This will have a positive impact on preparing patients, radiology employees, nurses and physicians for a smooth and easy transport to and from the MRI examination.

Objectives {6a}

The goal of this study is to assess whether early imaging with MRI (within 36 hours) after craniotomy has a different impact on patient stress compared to delayed imaging (between 36 and 72 hours). Secondly, we aim to assess whether there is a difference in patient stress level between postoperative MRI and CT performed within 72 hours postoperatively.

The authors hypothesize that delayed MRI imaging after craniotomy is more comfortable for patients without having negative implications on the validity and reliability of radiological assessments compared to imaging performed within 36 hours. Secondly, we hypothesize that postoperative MRI is more stressful for patients than postoperative CT.

Trial design {8}

The IPAST-CRANIO study (Evaluation of patient STress level caused by radiological Investigations in early Postoperative phase After CRANIOtomy) is a patient-oriented, prospective, exploratory cohort study.

Methods and Analysis

Study setting {9}

Data will be collected from patients between 18 and 80 years old who receive MRI or CT follow-up studies after craniotomy for resection of a space occupying lesion (benign or malignant) or vascular procedure at the Department of Neurosurgery at the University Hospital Zurich.

Eligibility criteria {10}

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- Written consent of the patient

- Age between 18 and 80 years
- Planned supra- or infratentorial (partial) resection of space occupying lesion (benign or malignant) or vascular neurosurgical procedure (clipping of an aneurysm, resection of an arteriovenous malformation/fistula, resection of cavernoma)
- Planned MRI or CT follow-up within 72 hours after surgery

The presence of any of the following exclusion criteria will lead to exclusion of the participant:

- No informed consent
- Surgery involving only one burr hole (e.g. biopsy) instead of craniotomy
- Not able to fill out the questionnaires due to cognitive impairment or aphasia
- Not German or English speaking
- Contraindication for MRI/CT examination
- No postoperative MRI or CT examination planned within 72 hours after surgery

Patient and Public Involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Who will take informed consent? {26a}

Patients will be informed verbally and in writing about the study by members of the study team. The information will be given at least one day before the surgical procedure to ensure enough time to consider participation. We emphasize that participation in the study does not impose a significant additional burden on patients as only short questionnaires need to be completed which do not entail any significant risks or unreasonable questions.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Furthermore, patients will be informed and educated in detail about other aspects:

- The intended further use of the non-genetic data for research purposes;
- Their right to refuse or withdraw consent at any time without justification;
- Their right to be informed of the results affecting their health and their right to waive this information;
- The measures taken to protect personal data;
- The possibility of sharing the personal data with third parties for research purposes.
- The collection of patients' consent will take place after the study has been approved by the Ethics Committee.

Interventions

Explanation for the choice of comparators {6b}

The authors hypothesize that the optimal period for postoperative imaging is 36 to 72 hours and therefore decided to include the early time frame (within 36 hours) as an adequate comparator. The authors will also compare the outcomes between the group undergoing postoperative CT and the group undergoing postoperative MRI.

Intervention description {11a}

In general, all patients in our institution receive postoperative imaging within the first 72 hours after a craniotomy for a space-occupying lesion or vascular procedure. The study intervention includes the completion of a questionnaire right before and after the postoperative radiological investigation (Figure 1). Patients are divided in two groups depending on the time interval between end of surgery and radiological investigation: late group (completing the questionnaire 36 to 72 hours after surgery) and early group (completing the questionnaire within 36 hours after surgery). The time intervals to the radiological investigation are assigned by coincidence and the patients are not randomized into any group. The exact time interval until examination depends on various factors, e.g.: capacity of the department of neuroradiology or weekday of surgery (patients operated on Friday are more likely to receive postoperative imaging on Monday; patients operated on Thursday are most likely receive it on Friday) and patient condition (early imaging will more likely be performed in suspected postoperative complications). We decided to use this way of defining the comparators as we are primarily interested in examining potential differences between groups, rather than assessing causality between delayed imaging and stress level.

The questionnaire consists of visual analog scale (VAS) for headache, visual analog scale (VAS) for nausea, and Body Part Discomfort Scale (Figures 2, 3 and 4). At the end of the questionnaire, patients will be asked to answer the following question:

In your opinion, should the MRI and/or CT scan have been performed earlier or later? The possible answers are:

- Yes, earlier;
- Yes, later;
- No, I am satisfied with the timing of the exam.

The authors have chosen these scales because they are validated and simple to understand and register. The completion of each questionnaire will take 5 to 10 minutes, and the burden for each patient is assumed to be low as the questionnaires do not contain any unreasonable questions.

Criteria for discontinuing or modifying allocated interventions {11b}

Although patients might have signed the informed consent situations that do not allow for completion of the questionnaires can occur. Reasons include postoperative complications leading to imaging in intubated patients, emergency imaging in extubated patients, or the neurosurgeon's decision not to perform postoperative imaging due to case-specific

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3 considerations. These patients will be excluded from analysis and the reason for not
4 completing the questionnaire will be registered.
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7 **Strategies to improve adherence to interventions {11c}**

8 This study is implemented in close and intensive collaboration with nursing staff and
9 supported by residents, medical students and administrative staff. Through this collaboration
10 the study team has managed to create sufficient resources ensuring a high and optimal
11 adherence to the intervention.
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14 **Relevant concomitant care permitted or prohibited during the trial {11d}**

15 None, the interval to radiological investigation will not be delayed due to completion of the
16 questionnaire.
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19 **Provisions for post-trial care {30}**

20 Participants will be informed about the results by an information letter, if interested. The
21 scheduling of future postoperative imaging will be planned based on this study's results.
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25 **Outcomes {12}**

26 The primary endpoint of the study is the difference in subjective stress after craniotomy
27 measured right before and after postoperative MRI or CT imaging with the mentioned
28 instruments. Subjective stress is evaluated as a combination of the scores VAS pain, VAS
29 nausea, and 0.5* Body Part Discomfort score (Figures 2, 3 and 4). A minimum score of 4.5
30 and a maximum score of 42.5 can be achieved.
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33 The secondary endpoints of the study are divided into two groups:
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35 1. Patient specific secondary endpoint:

- 36 • patient interpretation of whether MRI follow-up was performed at the correct interval.
37

38 2. Radiology specific secondary endpoints:

- 39 • residual tumor on MRI.
- 40 • contrast enhancement on MRI (postoperative reactive change, not tumor specific).
- 41 • significant post-operative bleeding.
- 42 • Infarction.
- 43 • residual perfusion of the aneurysm or AVM/AVF remnant.
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54 **Participant timeline (Figure 1) {13}**

55 Patients are screened on the hospital admission day by the study team and informed consent
56 is taken if inclusion criteria are fulfilled and if no exclusion criteria are met. Questionnaires
57 are completed by patients immediately before and after postoperative MRI or CT imaging.
58 The study is finished for each patient after having completed the post-investigational
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questionnaire. If either or both questionnaire(s) cannot be completed, the patient's study participating is finished after the radiological investigation. Radiological findings are assessed and documented in writing by a neuroradiologist according to local guidelines.

Sample size {14}

A sample measurement of VAS scores in 100 patients with craniotomy for tumour resection in 2019 resulted in a mean score of 1.8 (VAS pain) and 0.8 (VAS nausea). Because there was no baseline data for the Body Part Discomfort score, it was equated to the percentage of VAS pain per patient. This resulted in an average Body Part Discomfort score of 12.3 points. For calculating the total score, the VAS-scores and half of the points from the Body Part Discomfort score are used. The total mean score of all three measurements then becomes 13.6 (standard deviation 5.4). To measure an expected change of one third for the separate scores with a power of 80% and a type I error of 5%, a total of 224 patients are required for the study. To correct for any loss to follow-up, we will include 230 patients in this study.

Recruitment {15}

The study team screens all the patients on the admission day based on demographics, diagnosis and planned operation. All adult patients receiving craniotomy for a space occupying lesion or vascular indications are asked to participate in the study.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Data will be collected from all patients aged 18 to 80 years who receive postoperative MRI or CT follow-up after craniotomy for resection of a cerebral space-occupying lesion (benign and malignant) or vascular procedure using a questionnaire. Radiological findings are assessed and documented in writing by a neuroradiologist according to local guidelines.

The CRF collects the following information and scores:

- Demographic data of patients (sex, age)
- Localization of craniotomy (side, supra- or infratentorial, lobe and region)
- Time interval (in hours and postoperative day) between end of surgery and start of MRI or CT scan
- Indications for post operative imaging as per the surgeon
- Neuroradiology reports of postoperative imaging examinations
- Patient related criteria:
 - Visual analog scale (VAS) for headache (Figure 2).(9)
 - VAS for nausea (Figure 3).(9)

- Body Part Discomfort Scale (Figure 4)(10).

At the end of the second questionnaire, patients will be asked to answer the following question:

- In your opinion, should the MRI and/or CT scan have been performed earlier or later? The possible answers are:

- Yes, earlier;
- Yes, later;
- No, I am satisfied with the timing of the exam.

The radiological criteria that will be examined are as follows:

- Location of tumor (supra- or infratentorial, left or right)
- Tumor remnant on MRI
- Contrast enhancement on MRI (postoperative reactive change, not tumor-specific)
- Significant postoperative hemorrhage
- Postoperative infarction
- Residual perfusion of the aneurysm or AVM/AVF remnant

Plans to promote participant retention and complete follow-up {18b}

In this study, patients will complete a questionnaire before and after postoperative radiological examination. At the morning rounds, nursing staff is informed about patients who are planned for radiological examination and who are included in the study. When the nursing staff is informed about the exact time for the MRI or CT, the attending nurse (supported by a resident or a medical student if necessary) gives the questionnaire to the patient. The nurse is continuously reminded for this step, thanks to a comment in the digital patient report system (KISIM). Nursing staff and medical staff will monitor the completion of the questionnaires and can support at any time.

Data management {19}

Source data are available as paper questionnaires from patients and as digital documentation in the hospital-wide patient report system (KISIM) for clinical and radiological information. These data are pseudonymized, coded and stored in the form of the coded data in two Microsoft Access tables. One table contains the patient's hospital identification number, date of birth, and study number. The second Microsoft Access table contains all coded study data and patients are identified by study number only. Both tables are protected with passwords and are stored in a secured folder and are only accessible for study team members. Completed questionnaires are stored in a closed cabinet (available in research office and only accessible

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3 to the Project Leader of the study).
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6 7 **Confidentiality {27}**

8 Personal and medical data will be collected for this study. When data is collected for study
9 purposes, the data is pseudonymized and coded. The coding ensures that all reference data
10 that would reveal the identity of a patient (name, date of birth) is deleted and replaced by a
11 key. The list of keys always remains in the institution/hospital. In the case of a publication,
12 the summarized data cannot be traced back to an individual person. The name of a patient
13 will never appear on the internet or in any publication.
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17 18 19 **17. Data storage details**

20 The generation, transfer, storage, and analysis of health data within the scope of this project is
21 carried out in strict compliance with the current legal provisions for data in Swiss Protection
22 and is carried out according to the HRO regulation Art. 5.
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24 All persons who have access to patient data within the scope of the study are subject to the
25 obligation of confidentiality.
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28 It is possible that the study will be reviewed by the ethics committee or by the institution that
29 initiated the study. The investigator may have to disclose personal and medical data for such
30 controls. All persons must maintain absolute confidentiality.
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33 34 35 **Statistical methods**

36 37 **Statistical methods for primary and secondary outcomes {20a}**

38 For data analysis, patients are being divided into 2 groups based on predefined time intervals:
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- 40 1. early imaging: within 36 hours postoperatively.
- 41 2. late imaging: between 36 and 72 hours postoperatively.
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45 A second analysis is performed, dividing patients into the following groups:
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- 47 1. early imaging: on the same day of surgery (day 0) or 1st postoperative day.
- 48 2. late imaging: on the 2nd or 3rd postoperative day.
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53 A third analysis will be performed, dividing the patients based on the radiological
54 examination performed (MRI or CT).
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57 Descriptive data will be investigated for a normal distribution. In case of a normal
58 distribution, results will be presented as means with standard deviations and groups compared
59 by Chi-square tests. If not, the results will be presented as medians with interquartile ranges
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3 and results of a non-parametric (Fisher's exact test) will be reported. Results of pre- and post-
4 imaging questionnaires are compared with the paired t-test, or Wilcoxon signed rank test in
5 case of a non-normal distribution of data. The primary outcome is assessed by subtracting the
6 mean subjective stress score before the investigation from the score after the investigation.
7 Crude and adjusted stress score differences are calculated in relation to the predefined time
8 interval groups with logistic regression analysis. Confounders are considered when the
9 change in stress score is >10% in the stratification for the respective parameter. A
10 multivariable regression analysis is performed, adjusting for confounders. A secondary
11 analysis is done by calculating the relative change in stress score before and after the
12 investigation and their corresponding 95% confidence interval (CI), with multivariable
13 regression analysis with confounders as described above.

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Secondary endpoints are reported unadjusted with corresponding 95% CI.

A p-value of <0.05 is considered a significant difference. All analyses are done using STATA
16.1 or higher (StataCorp LLC, Texas, USA).

Interim analyses {21b}

No interim analyses are planned due to the low risk of the study intervention and an assumed
minimal burden to the patients.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Postoperative complications requiring postoperative imaging in intubated patients unable to
complete the questionnaire and emergency imaging in extubated patients with relevant time
and personnel limitations are criteria for not performing the questionnaire. Furthermore,
questionnaires will not be performed in case the surgeon decides not to perform postoperative
imaging. These situations are defined as protocol deviations and these patients will be
excluded from analysis.

If only the data before postoperative imaging (only part of the questionnaire before
radiological examination fulfilled) are acquired and post-imaging data are missing, these
collected data will only be used in the baseline characteristics and not in the analysis of the
primary outcome. However, if the collected data include secondary outcomes, they will be
included into the secondary data analysis.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

We aim to publish the full study protocol in a peer-reviewed medical journal. Full access is
granted to the original protocol and participant level-data after consideration with the
corresponding author. The statistical code is written in STATA (StataCorp LLC, Texas,
USA) and available upon request.

Oversight and monitoring

No external monitoring is planned due to the low risk of the intervention (questionnaire) and an assumed small burden for study participants. Internal monitoring by the project leader and study coordinator is performed after including the first 10% of patients.

Adverse event reporting and harms {22}

Participation in the study includes only the completion of a questionnaire, in which we do not expect to encounter (serious) adverse events ((S)AE). Nevertheless, if an (S)AE occurs, the project leader and the sponsor will be notified within 24 hours and decide if immediate safety and protective measures have to be taken during the conduct of the research project. The Ethics Committee will be notified of these measures and of the underlying circumstances via BASEC within 7 days.

Frequency and plans for auditing trial conduct {23}

The department of neurosurgery of the USZ undergoes a research audit every five years to guarantee high quality of the conducted scientific research. Due to the low risk of the current study, no additional study specific audit is planned.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

Substantial changes to the project set-up, the protocol, and relevant project documents will be submitted to the Ethics Committee for approval according to HRO Art. 18 using the BASEC system. The study team and nursing staff will be informed by oral information and email about important protocol changes.

Ethics and dissemination {31a}

The final decision on the publication of the results will be made by the sponsor (Luca Regli) and the project leader (Menno R. Germans). The authors are planning to publish the data of this study in a peer-reviewed paper. After database closure, the data will be exported to the local data repository (Zurich Open Repository and Archive) of the University of Zurich. Authors of the publication are persons who conceived and planned the study or performed parts of the statistical analysis. Unless Luca Regli and Menno R. Germans decide otherwise, Lazar Tomic is the first author and Menno R. Germans is the last author. Joint first or last authorship may be decided if other investigators qualify appropriately by spending a large

amount of time and effort on the study. All data belong to Luca Regli and Menno R. Germans, who will decide on authorship, order of authors, journals to be published, and partial results and aspects of the final analysis.

In consultation with Luca Regli and Menno R. Germans, parts of the study results may be analyzed separately by the participating investigators; for these analyses and publications, the first and last authors as well as the order of authorship will be determined by the sponsor, project leader and the principal investigator of the subproject.

The institutional review board (Cantonal Ethics Committee Zürich) approved this study on 4th of August 2020 under case number: BASEC 2020-01590, Protocol version: 1.0; Protocol date: 25.06.2020.

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Declarations

Authors' contributions

Study concept and initiation: Menno R. Germans, Lazar Tomic and Luca Regli

Data collection: Marco Thoma, Stefanos Voglis, Delal Bektas, Anna-Sophie Hofer and Atina

Pangalu

Data analysis: Lazar Tomic, Menno R. Germans

Writing manuscript: Lazar Tomic, Menno R. Germans

Critically reviewing manuscript: all authors

Funding

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Competing interests

None to declare

Trial status

Patient recruitment started on September 20th 2020. Until February 5th 2022 we had recruited 120 participants. With the current inclusion rate, we expect to have the final data in January 2023.

Abbreviations

BASEC Business Administration System for Ethical Committees

CRF Case report form

FOPH Federal Office of Public Health

HRA Human Research Act

HRO Human research ordinance

MRI Magnetic resonance imaging

VAS Visual analogue scale

CT Computed tomography

AVM Arteriovenous malformation

AVF Arteriovenous fistula

USZ University Hospital Zurich

Availability of data and material

The data is encrypted and entered into Microsoft Access study-specific patient ID, which is password protected and stored on the hospital servers of the University Hospital Zurich.

Access to the data for the other colleagues in the department of Neurosurgery of the University Hospital Zurich can only be granted by the project leader and in case of participation in the study team. After database closure, the data will be exported to the local data repository (Zurich Open Repository and Archive) of the University of Zurich.

Ethics approval and consent to participate

The institutional review board (Kantonale Ethikkommission Zürich) approved this study on 4th of August 2020 under case number: BASEC 2020-01590, Protocol version: 1.0; Protocol date: 25.06.2020.

Consent for publication

All participants gave their written consent for publication (Informed consent version 1.0; informed consent date 14.08.2020).

Figures

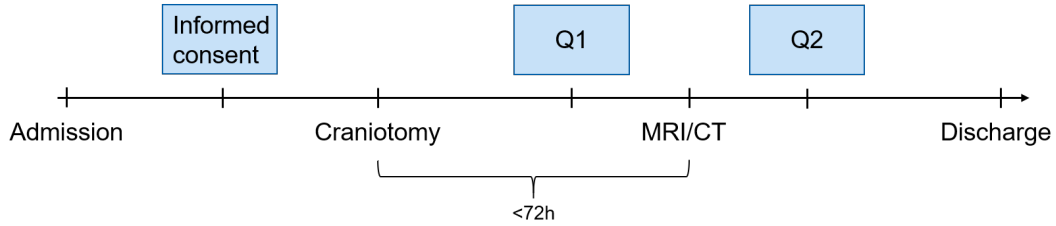
Figure 1: Participant timeline ; Q1: pre-imaging questionnaire assessing headache, nausea, and discomfort; Q2: post-imaging questionnaire assessing headache, nausea, discomfort, and timing of imaging

Figure 2: Visual analog scale (VAS) for headache

Figure 3: Visual analog scale (VAS) for nausea

Figure 4: Body Part Discomfort Scale

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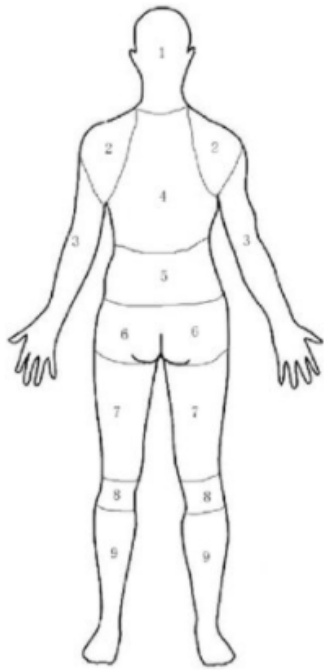
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4 **no** 0 1 2 3 4 5 6 7 8 9 10 **strongest** headache
5 headache I can imagine
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| no | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | strongest | nausea |
| nausea | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | I can imagine |

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1 Not uncomfortable 4 Very uncomfortable
2 Barely uncomfortable 5 Extremely uncomfortable
3 Quite uncomfortable

1 Head and neck



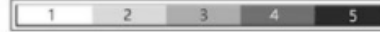
2 Shoulder



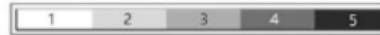
3 Arm



4 Middle back



5 Low back



6 Buttock



7 Thigh



8 Knee



9 Leg and foot



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