


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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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 tumour 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 with 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 18–80 years who receive postoperative MRI or CT imaging following a craniotomy for resection of a cerebral tumour (benign and malignant) or vascular surgery. Participants have to complete questionnaires containing visual analogue scores (VAS) for headache and nausea, 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* Body Part Discomfort core.

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.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Prospective.
- ⇒ Patient-oriented study design.
- ⇒ Large number of participants with predefined sample size calculation.
- ⇒ Single-centre study.
- ⇒ No randomisation of participants.

The sponsor (LR) and the project leader (MR.G) 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 LT. The data are not publicly available due to privacy/ethical restrictions.

Trial registration number NCT05112575; ClinicalTrials.gov.

INTRODUCTION

MRI after neurosurgical resection of a cerebral tumour is usually performed in the first 72 hours after surgery.^{1–5} Accurate assessment of early postoperative resection status of brain tumours is mandatory for further treatment planning, for example, delineation of the radiation field during radiotherapy or reoperation for significant residual tumour.⁶ Various MRI sequences provide information on tumour size and location as well as additional insight into secondary phenomena such as oedema, haemorrhage, infarct, necrosis and signs of increased intracranial pressure.^{1 3 6 7} The 72-hour 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.¹⁷ Postsurgical repair mechanisms at the resection site resulting from hypervascularisation 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 oedema. 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 CT, which may be less stressful for patients as it takes only 5 min to 10 min 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-centred 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 optimisation 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

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 with delayed imaging (between 36 hours and 72 hours). Second, 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 hypothesise that delayed MRI after craniotomy is more comfortable for patients without having negative implications on the validity and reliability of radiological assessments compared with imaging performed within 36 hours. Second, we hypothesise that postoperative MRI is more stressful for patients than postoperative CT.

Trial design

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

METHODS AND ANALYSIS

Study setting

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

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 supratentorial 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 (eg, 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?

Patients will be informed verbally and in writing about the study by members of the study team. The information will be given at least 1 day before the surgical procedure to ensure enough time to consider participation. We emphasise that the 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

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

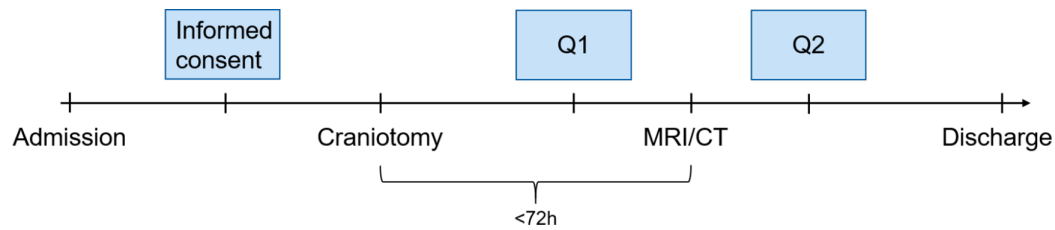


Figure 1 Participant timeline; Q1: pre-imaging questionnaire assessing headache, nausea, and discomfort; Q2: post-imaging questionnaire assessing headache, nausea, discomfort and timing of imaging.

- ▶ 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

The authors hypothesise that the optimal period for post-operative imaging is 36 hours 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

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 into 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 randomised into any group. The exact time interval until examination depends on various factors, for example, 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 analogue scale (VAS) for headache, VAS for nausea and Body Part Discomfort Scale (figures 2–4). 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 examination.

The authors have chosen these scales because they are validated and simple to understand and register. The completion of each questionnaire will take 5 min to 10 min, 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

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 completing the questionnaire will be registered.

Strategies to improve adherence to interventions

This study is implemented in close and intensive collaboration with nursing staff and supported by residents, medical students and administrative staff. Through this collaboration, the study team has managed to create sufficient resources ensuring a high and optimal adherence to the intervention.

Relevant concomitant care permitted or prohibited during the trial

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

Provisions for post-trial care

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

no 0 1 2 3 4 5 6 7 8 9 10 strongest headache
headache I can imagine

Figure 2 Visual analogue scale (VAS) for headache.

Outcomes

The primary endpoint of the study is the difference in subjective stress after craniotomy measured right before and after postoperative MRI or CT imaging with the mentioned instruments. Subjective stress is evaluated as a combination of the scores VAS pain, VAS nausea and 0.5* Body Part Discomfort Score (figures 2–4). A minimum score of 4.5 and a maximum score of 42.5 can be achieved.

The secondary endpoints of the study are divided into two groups:

1. Patient-specific secondary endpoint:
 - Patient interpretation of whether MRI follow-up was performed at the correct interval.
2. Radiology-specific secondary endpoints:
 - Residual tumour on MRI.
 - Contrast enhancement on MRI (postoperative reactive change, not tumour specific).
 - Significant postoperative bleeding.
 - Infarction.
 - Residual perfusion of the aneurysm or arteriovenous malformation and arteriovenous fistula remnant.

Participant timeline

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 (figure 1). 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 postinvestigational 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

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 (SD 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

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

Data will be collected from all patients aged 18–80 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 case report form (CRF) collects the following information and scores:

- ▶ Demographic data of patients (sex, age).
- ▶ Localisation of craniotomy (side, supratentorial 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 postoperative imaging as per the surgeon.
- ▶ Neuroradiology reports of postoperative imaging examinations.
- ▶ Patient-related criteria:
 - 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 0 1 2 3 4 5 6 7 8 9 10 strongest nausea
nausea I can imagine

Figure 3 Visual analogue scale (VAS) for nausea.

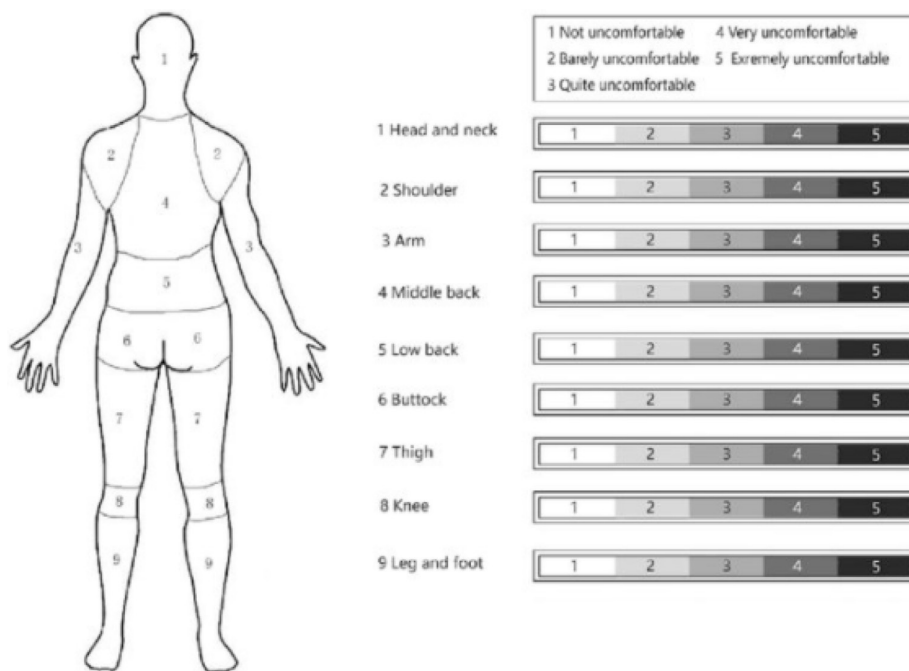


Figure 4 Body Part Discomfort Scale.

- No, I am satisfied with the timing of the examination. The radiological criteria that will be examined are as follows:

- ▶ Location of tumour (supratentorial- or infratentorial, left or right).
- ▶ Tumour remnant on MRI.
- ▶ Contrast enhancement on MRI (postoperative reactive change, not tumor-specific).
- ▶ Significant postoperative haemorrhage.
- ▶ Postoperative infarction.
- ▶ Residual perfusion of the aneurysm or AVM/AVF remnant.

Plans to promote participant retention and complete follow-up

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, Cistec AG, Switzerland). Nursing staff and medical staff will monitor the completion of the questionnaires and can support at any time.

Data management

Source data are available as paper questionnaires from patients and as digital documentation in the hospitalwide patient report system (KISIM) for clinical and radiological information. These data are pseudonymised, 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

Personal and medical data will be collected for this study. When data are collected for study purposes, the data are pseudonymised 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 summarised data cannot be traced back to an individual person. The name of a patient will never appear on the internet or in any publication.

Data storage details

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

All persons who have access to patient data within the scope of the study are subjected to the obligation of confidentiality.

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



Statistical methods

Statistical methods for primary and secondary outcomes

For data analysis, patients are being divided into two 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 first postoperative day.
2. Late imaging: on the second or third 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 SD and groups compared by χ^2 tests. If not, the results will be presented as medians with IQRs and results of a non-parametric (Fisher's exact test) will be reported. Results of preimaging and postimaging 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% 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 V.16.1 or higher (StataCorp LLC, Texas).

Interim analyses

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

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 postimaging 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

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) and available on 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

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 whether 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

The department of neurosurgery of the University Hospital Zürich undergoes a research audit every 5 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 (eg, trial participants, ethical committees)

Substantial changes to the project setup, 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

The final decision on the publication of the results will be made by the sponsor (LR) and the project leader (MR.G). 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 LR and MR.G decide otherwise, LT is the first author and MR.G 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 LR and MR.G, who will decide on authorship, order of authors, journals to be published and partial results and aspects of the final analysis.

In consultation with LR and MR.G, parts of the study results may be analysed 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.

Contributors Study concept and initiation: MRG and LT. Data collection: MT, SV, DB, ASH and AP. Data analysis: LT, MRG. Writing manuscript: LT, MRG. Critically reviewing manuscript: all authors.

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Competing interests None declared.

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Patient consent for publication Not applicable.

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Data availability statement All the data of this study are available upon reasonable request.

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