Standard Operating Procedure (SOP)

Neurovascular toxicities

WP2 – Task 2.4, HARMONIC-RT

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1.0	21.01.2021	AUH-Team	

Table of Contents

1. Objectives

The purpose of this Standard Operating Procedure (SOP) is to describe the workflow in the neurovascular task of the prospective part of the HARMONIC study.

2. Background

Neurovascular late effects after radiotherapy for childhood brain tumors are not well described in the literature. The neurovascular damage following irradiation can be divided into small or large vessel disease. MRI changes characteristic for small vessel diseases are microbleeds, lacunar infarcts and white matter hyperintensities. These image changes are similar to those seen in elderly non-irradiated patients As seen in the geriatric population, these changes can be associated with neurocognitive decline. Another aspect of small vessel disease after radiotherapy is the formation of cavernomas, which is believed to be caused by neoangiogenesis after damage to the small vessels of the brain. Long-term survivors of pediatric brain tumors are also at an increased risk of cerebrovascular accidents compared to the general population due to large vessel atheropathy. Damage to the central arteries at the base of the brain may lead to stenosis or occlusion of these large vessels, in a manner similar to the inflammation characteristic for Moya Moya disease. Clinically patients with large vessel disease may present with transient ischemic attacks, intracranial hemorrhages or ischemic strokes. Endothelial and glial damages can also be lead to radiation necrosis in the brain parenchyma.The risk of developing a cerebrovascular accident is likely related to the radiation doses received in specific neurovascular structures.

In this prospective study, we will investigate and validate the extent and risk factors related to neurovascular events, quantify radiation dose-volume relationships in neurovascular structures for development of neurovascular pathologies, and explore imaging changes as a precursor for neurovascular events. These will be also set in relation to the patient's quality of life and vascular biomarkers in patients also participating in WP5 and WP2 task 2.6.

3. Participating Centers

AUH, GR, KUL, UK Essen

Waiting for confirmation from UCAEN

4. Inclusion / Exclusion Criteria

Inclusion Criteria:

- Patient included in the prospective part of HARMONIC
- Tumour in the brain or in the base of skull
- Possibility of MRI with neurovascular sequences in follow-up

Exclusion Criteria:

- Diffuse pontine glioma
- High grade glioma
- Previous irradiation in the brain

5. Definition MRI with neurovascular sequences (*nv* MRI)

***nv*MRI:**
Standard tumour follow up MRI including T1 with and without contrast, T2 or Flair, DWI

with added sequences: SWI or T2 STAR, MR-Angio or TOF

(in Aarhus the Black Blood sequence will also be added)

Please note that **the MRI sequences between institutions will not be harmonized**. Every institution will perform their MRIs as ususal in the clinical routine and the neurovascular sequences will be added after the MRI protocol that the single institution uses. We will collect technical informations about the specifications about the MRI sequences used in the different institutions.

6. Data necessary to collect

- Radiation dose plans
- MRIs
    - **Mandatory MRIs**: Last diagnostic MRI before RT, *nv*MRI 1 year, 3 years, 5 years after RT
    - Optional MRIs: Planning *nv*MRI for simulation of RT, *nv*MRI M120 after RT (protocol needs amendment for this)
    - The radiological reports of the institution should also be uploaded into the eCRF or into Aquilab in a pseudonymised way.
- Baseline and Clinical follow up M12, M36 and M60 in the HARMONIC eCRF in the neurovascular section (if amended af M120 will be added later)
- If available vascular markers from WP5
- If available QoL/fatigue/academic achievement from task 2.6.

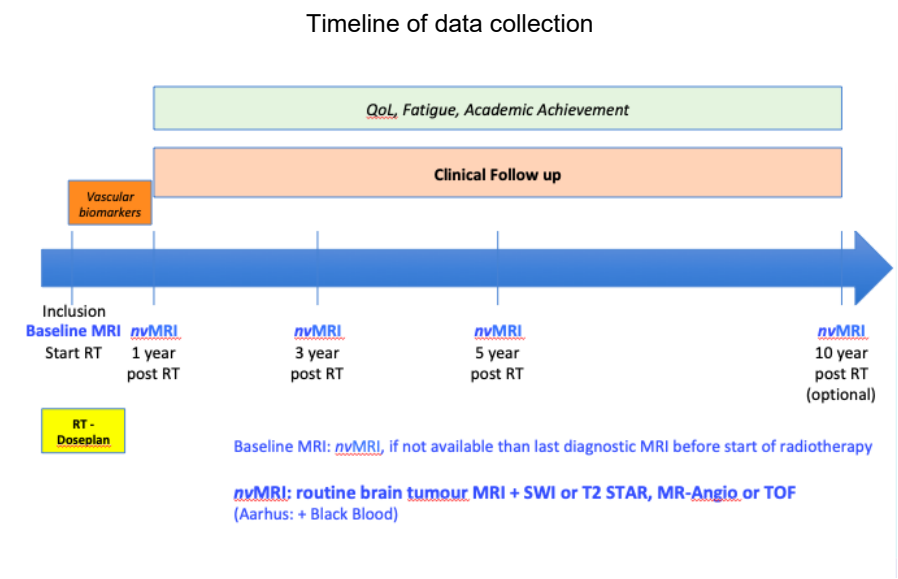

Figure 1: Timeline of data collection in the individual patient

7. Patient inclusion

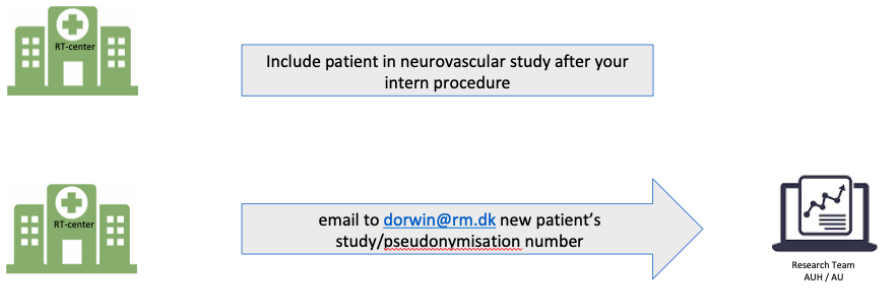

Figure 2: Information to AUH about patient inclusion into the neurovascular task

8. Data collected by the participating institutions

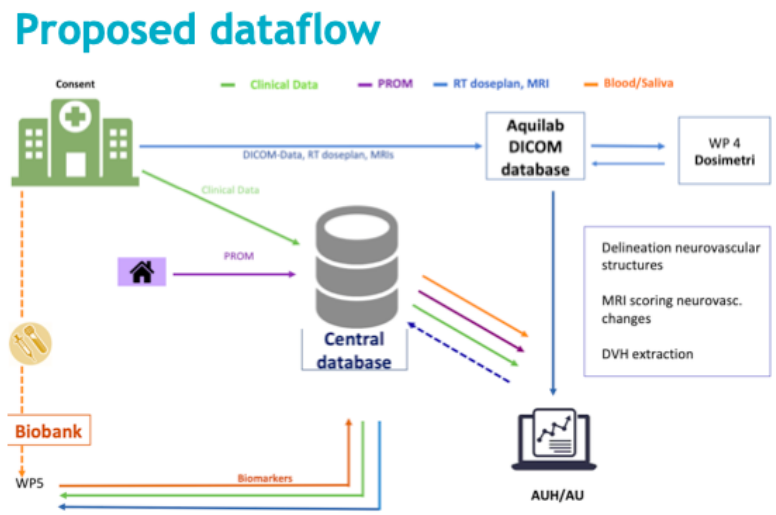

Figure 3: Proposed dataflow, PROM stands for task 2.6 QoL, Fatigue, Academic Achievement

8.1. Uploading of data to Aquilab database and update of eCRF for the neurovascular Task

Kommenterede [TT1]: How DICOM file will be sent to AQUILAB?

All DICOM data, in any form, that are uploaded to the Aquilab platform will be identified only by the ***Participant Study ID***

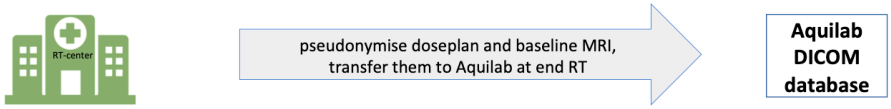

Figure 4: Uploading of RT dose plan and Baseline MRIs

- Patient's baseline MRI (last diagnostic MRI before RT) and if available *nv*MRI done for RT planning (optional) at simulation and the radiation doseplans should be uploaded at the end of radiotherapy (latest at 3 months after RT) to the Aquilab database. Upload also the pseudonymised radiological report of the uploaded MRI. Please upload these items regularly so that we can in a good timely manner delineate the neurovascular structures. It is important that all DICOM material that is uploaded to Aquilab is pseudonymised with the patient's unique HARMONIC Participant ID and without any other patient identifiers. The Participants ID will be known to the including center. The procedure of uploading MRIs and dose plans is not yet clearly defined as we do not have access to the Aquilab database right now. This part of the SOP will be updated as soon as this access is established, but the procedure will be probably also defined by WP4.

If your institution does not have access to Aquilab, please inform us before start of the study in your clinic, so that we can find another solution for accession of MRIs and doseplans.

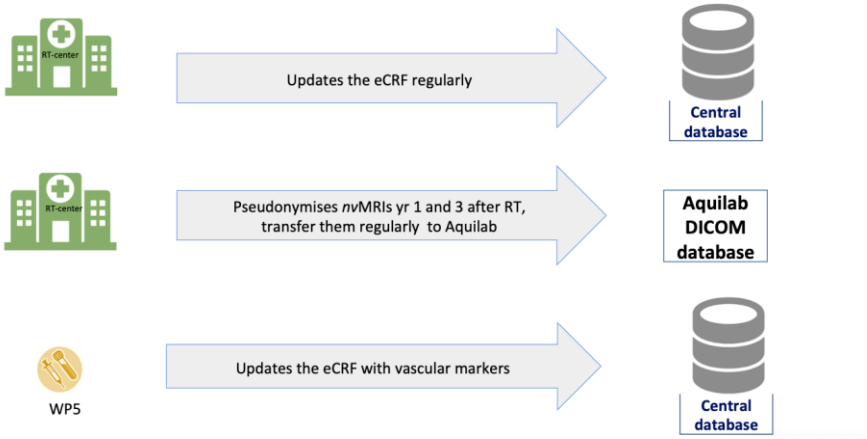

Figure 5: collection of follow up data

In the follow up you need to organize the *nv*MRIs at your institution, probably you will need to involve the pediatric oncologists who do the follow up.

Timeintervals: there is a margin of +/- 3 months to the individual timepoints:

*nv*MRI 1 year after RT: corresponds to 9-15 months after RT

*nv*MRI 3 years after RT: corresponds to 33-39 months after RT

*nv*MRI 5 years after RT: corresponds to 57-63 months after RT

Please upload the MRIs and the radiological reports latest three months after acquisition, but earlier if somehow possible so that we can analyse as much data as possible for the final report in 2024. The same is also important for update of the eCRF and the vascular markers, if available.

8.2. Updating of the neurovascular eCRF

Please update the neurovascular eCRF regularly and as near as possible to the M12, M36, M60 timepoint as possible and not earlier or later than three months before or after, ideally the clinical eCRF is updated at the time of the MRI. In the eCRF **all events that have happened since the last timepoint** need to be filled out.

In the **Baseline** eCRF neurovascular disease you have to fill out, if applicable:

- Neurological symptoms
  - Numbness
  - Weakness of limbs
  - Vertigo
  - Problems with balance
  - Problems with coordination
  - Cranial Nerve Dysfunction
  - Speechprlbems
  - Visual Problems
  - Seizures
  - Headaches
    - Severe Headaches
    - Vascular Headache / Migraine
  - Others

- Clinical Signs of neurovascular disease (with date of diagnosis)
  - Stroke
  - Bleeding
  - TIA (transitional Ischemic Attack)
  - PRIND (prolonged reversible ischemic neurological disorder

- MRI diagnosis (with date of diagnosis)
  - Stroke
  - Bleeding
  - Moya-Moya Disease

- CT diagnosis (with date of diagnosis)
  - Stroke
  - Bleeding

In the Follow up eCRF neurovascular task at M12, M36, M60 and M120 (if amended) you will need to fill out if applicable:

- New Neurological symptoms
  - Numbness
  - Weakness of limbs
  - Vertigo
  - Problems with balance
  - Problems with coordination
  - Cranial Nerve Dysfunction
  - Speechprlbems
  - Visual Problems
  - Seizures
  - Headaches
    - Severe Headaches
    - Vascular Headache / Migraine
    - SMART syndrome (Stroke Like Migraine Attacks after Radiotherapy)
  - Others

- Aggravation of existing neurological symptoms
  - Numbness
  - Weakness of limbs
  - Vertigo
  - Problems with balance
  - Problems with coordination
  - Cranial Nerve Dysfunction
  - Speechproblems
  - Visual Problems
  - Seizures
  - Headaches
    - Severe Headaches
    - Vascular Headache / Migraine
    - SMART Syndrome (Stroke Like Migraine Attacks after RT)
  - Others

- Clinical Signs of neurovascular disease (with date of diagnosis)
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- MRI diagnosis (with date of diagnosis)
  - Stroke
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  - Moya-Moya Disease

- CT diagnosis (with date of diagnosis)
  - Stroke
  - Bleeding

8.3. Updating of the vascular markers

The team of WP5 will update the vascular markers important for neurovascular events, these are not yet clearly defined. Correlation of clinical symptoms and image markers will be further discussed with WP5

8.4. Correlation of QoL, Fatigue, Academic Achievement

This correlation will be further discussed with the team of task 2.6.

9. Data collected by AUH

Our team at AUH will at regular time intervals delineate the neurovascular structures and review the MRIs, we will transfer the DVH information and the imaging marker results back to the central database.

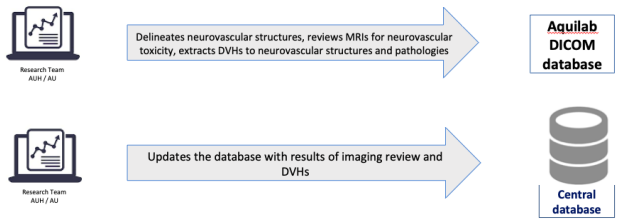

Figure 6: Analysis of data by AUH team

9.1. Neurovascular structures and DVHs used in the study

The following structures will be delineated by the AUH team on all RT doseplans and DVHs will be extracted for the The brainstem DVH has been added as brainstem dose can important when looking at fatigue to be able to discern between brainstem RT fatigue and probable neurovascular fatigue. Together with the neuroradiologists we will estimate the dose received in areas of neurovascular image changes.

Dmean, Dmax, V%10,20,30,40,50Gy:

- Circle of Willis
- Suparcellar Cistern
- Chiasm
- Internal Carotid Artery ICA_L, ICA_R
- Middle Cerebral Artery MCA_L, MCA_R
- Anterior Cerebral Artery ACA_L, ACA_R
- Posterior Cerebral Artery PCA_L, PCA_R
- Anterior communcans Artery AComA_L, AComA_R
- Posterior communicans Artery PComA_L, PComA_R
- Basilary Artery BA
- *Brainstem*

Dmean, Dmax, V%10,20,30,40,50Gy, Vcc 10,20, 30, 40, 50 Gy:

- Whole Brain
- Neurovascular pathologies

9.2. Image markers scoring system used in this study

The following image markers for neurovascular disease will be reviewed by the neurovascular radiology team at AUH:

- Large vessel disease
  - Stenosis
    - No stenosis
    - < 50% stenosis
    - > 50% stenosis
    - Stenosis location
      - ICA, MCA, ACA, PCA, AComA, PComA, BA
  - Arterial Wall Enhancement
    - Not visible
    - Visible
    - If visible location
      - ICA, MCA, ACA, PCA, AComA, PComA, BA
- Cerebral Cavernoma
  - None
  - Present
    - Number of cavernoma
    - Location
      - Frontal, temporal, occipital/parietal, infratentorial, midbrain/sublobar, white matter, grey matter
- Small Vessel Disease
  - White Mater Lesions (Fazeka Score)
    - Perivenrtricular White matter
      - 0 (absent), 1 (caps of pencil thin lining), 3 (irregular periventricular signal)

- Deep White Matter
  - 0 (absent), 1 (punctate foci), 2(beginning confluence), 3 (large confluent areas)

➢ Cerebral Microbleeds
- None
- Present
  - Number of microbleeds
  - Location
    - ♦ Frontal, temporal, occipital/parietal, infratentorial, midbrain/sublobar, white matter, grey matter

➢ Lacunar Infarcts
- None
- Present
  - Number of lacunar infarcts
  - Location
    - ♦ Frontal, temporal, occipital/parietal, infratentorial, midbrain/sublobar, white matter, grey matter

➢ Enlarged Perivascular Spaces
- None
- < 10 (mild)
- 10-25 (moderate)
- > 25 (severe)

➢ Total score Small Vessel Disease

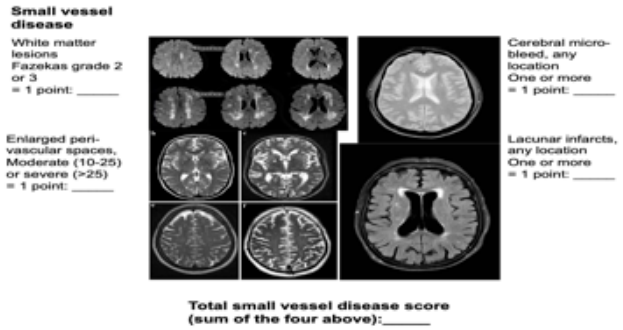

Figure 7: Scoring of Small Vessel disease

10. Analysis of and reporting of results

For the final HARMONIC report in june 2024, we will correlate the early neurovascular clinical toxicity with imaging markers, the serological markers dose to the neurovascular structures and QoL/fatigue/academic achievement data from task 2.6.

We would like to organize a scientific conference on neurotoxicity after RT approximately in april 2024 to present our results and discuss the further research in the neurovascular task.

We will be elaborating together with all WP2 partners and WP5 the HARMONIC report on the neurovascular toxicity.

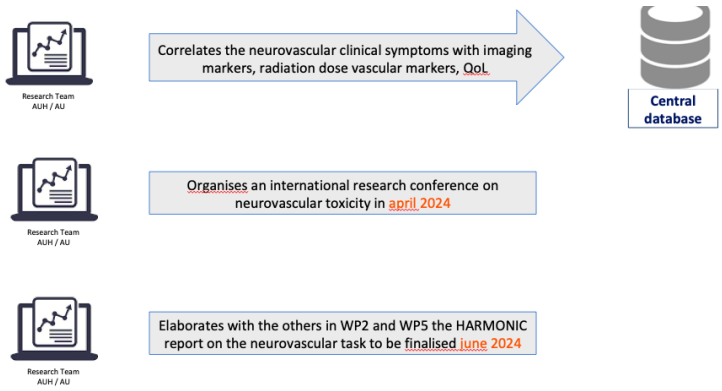

Figure 8: Elaboration of the final Report

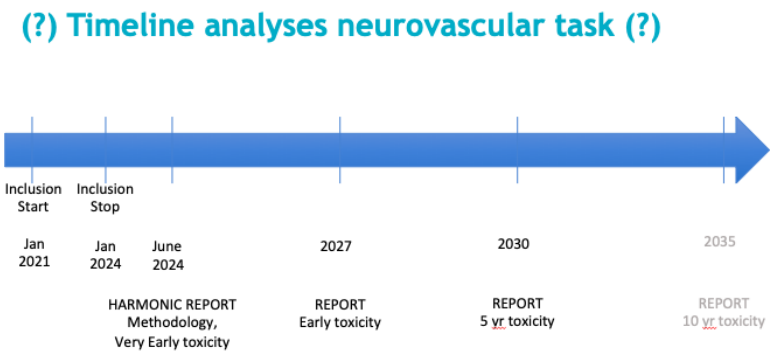

Figure 9: Approximate Timeline of reporting in the neurovascular task