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Original Article

REMIT: Reirradiation of Diffuse Midline Glioma Patients —A Nordic Society of Paediatric Haematology and Oncology Feasibility Study

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Abstract

Diffuse midline glioma (DMG) continues to be an aggressive brain stem cancer among children and young adults. It has a dismal prognosis, with less than 10% of patients alive two years after diagnosis. Radiotherapy has been demonstrated to be effective, albeit transient. Hence, radiotherapy is considered a cornerstone in the treatment. Reirradiation has, in retrospective studies, shown promising overall survival and palliative effect, but no pan-European consensus for reirradiation exists. The REMIT (**Re**irradiation of diffuse **Mi**dline glioma pa**T**ients) protocol evaluates safety and the palliative efficacy of reirradiation of patients with DMG (clinicaltrials.gov NCT06093165). Patients included in the protocol will be followed with 1) performance status (Karnofsky or Lansky), 2) toxicity monitored with Common Terminology Criteria for Adverse Events (CTCAE), 3) motor and functioning skill with PEDI-CAT (The Pediatric Evaluation of Disability Inventory) and 4) quantification of corticosteroid use. Furthermore, the impact on quality of life and well-being will be assessed qualitatively with interviews as well as with the Pediatric Quality of Life Inventory (PedsQl) Cancer Module questionnaire. The protocol also includes dose accumulation and contouring studies to assess standardization as well as a prescreening log to address selection bias of patients. The safety and palliative efficacy of reirradiation in DMG will be prospectively evaluated, including qualitative patient reported outcomes, through the REMIT protocol. REMIT is planned to open for inclusion in 2024.

Key words: Diffuse midline glioma; paediatric cancer; radiotherapy; reirradiation

Background

Diffuse midline glioma (DMG) is a rare yet highly aggressive type of brain cancer among children and young adults [1–3]. It has a dismal prognosis and less than 10% of patients are alive two years from diagnosis [1]. Radiotherapy provides a median time to progression of approximately three to six months and is currently considered the cornerstone in the treatment of DMG [4–6]. As the disease virtually always will progress, it is essential to optimize palliation with a focus on symptom relief, minimize the side effects of supportive medicines, reduce side effects of treatment, and improve quality of life for both patients and their families.

Previous studies have indicated a palliative effect and improvement in overall survival (OS) after reirradiation for progressive DMG [7,8]. Yet there is no pan-European consensus or recommendations available [7,9]. The primary radiotherapy course is often 54 Gray (Gy) in 30 fractions (F), which is also the recommended radiotherapy regimen in the international BIOMEDE 2 trial (clinicaltrials.

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gov NCT05476939). For reirradiation of DMG, a meta-analysis concluded that 20Gy/10F appeared to be safe regarding acute toxicity, including radionecrosis [9]. Due to the aggressive clinical course of DMG, patients will rarely live long enough to experience late effects. Hence, a systematic, protocol-driven approach to reirradiation with close follow-up of clinical performance status and quality of life is crucial for improving treatment outcomes and accessibility for this patient group [10].

The REMIT (**RE**irradiation of diffuse **MI**dline glioma pa**T**ients) study standardizes and explores the safety and the palliative efficacy of reirradiation of patients with DMG (clinicaltrials.gov NCT06093165). The study aims to offer a reirradiation regimen for patients with progressing DMG following primary radiotherapy. REMIT is an add-on to the BIOMEDE 2.0 trial but may also stand alone.

Methods and Study Design

Aims and Hypothesis

The primary objective of the REMIT protocol is to evaluate the safety of reirradiation.

Hypothesis 1. Reirradiation does not induce severe acute toxicity (grades 4–5).

The primary endpoint is the cumulative incidence of radiotherapy-related grade ≥4 CTCAE (The NCI Common Terminology Criteria for Adverse Events, version 5) events from initiation until 4 weeks after the last day of reirradiation.

This will be assessed by repeated adverse event assessment at baseline, 1 week after start of reirradiation, at the end of reirradiation, and every second week after reirradiation.

The secondary objective of REMIT is to prospectively assess the palliative efficacy of reirradiation of DMG.

Hypothesis 2. Reirradiation increases overall survival with 2–4 months and can offer symptom relief or disease control 4 weeks after reirradiation.

Palliative efficacy is evaluated by two endpoints: overall survival and symptom relief.

Overall survival will be calculated from the date of diagnosis to the date of death from any cause. Disease control will be calculated as time from the first day of reirradiation to the date of first radiological and/or clinical progression after reirradiation. The time from progression after reirradiation to the date of death by any cause will also be reported. Symptom relief will be evaluated by 1) clinical performance status (Karnofsky (KPS) or Lansky (LPS)), 2) a modified Pediatric Evaluation of Disability Inventory (PEDI) score, 3) daily steroid dose assessed, and 4) quality of life (QOL) assessed with the Pediatric Quality of Life Inventory (PedsQL) Cancer Module questionnaire, cf. Figure 1.

Follow-up

Toxicity

Toxicities will be assessed and graded according to CTCAE version 5.0 [12]. Toxicities will be registered 1 week after the start of reirradiation, at the end of reirradiation and every second week until death. After 4 months, the frequency of the toxicity scoring will be reduced to a monthly scoring. The relation to reirradiation will be addressed for each CTCAE symptom registered.

Performance Status

LPS/KPS will be reported at baseline, during reirradiation, at the end of reirradiation, and every second week until death. LPS or KPS should not take the neurological deficits per se into account. For children under 12 years of age, LPS will be used, and KPS for patients older than 12.

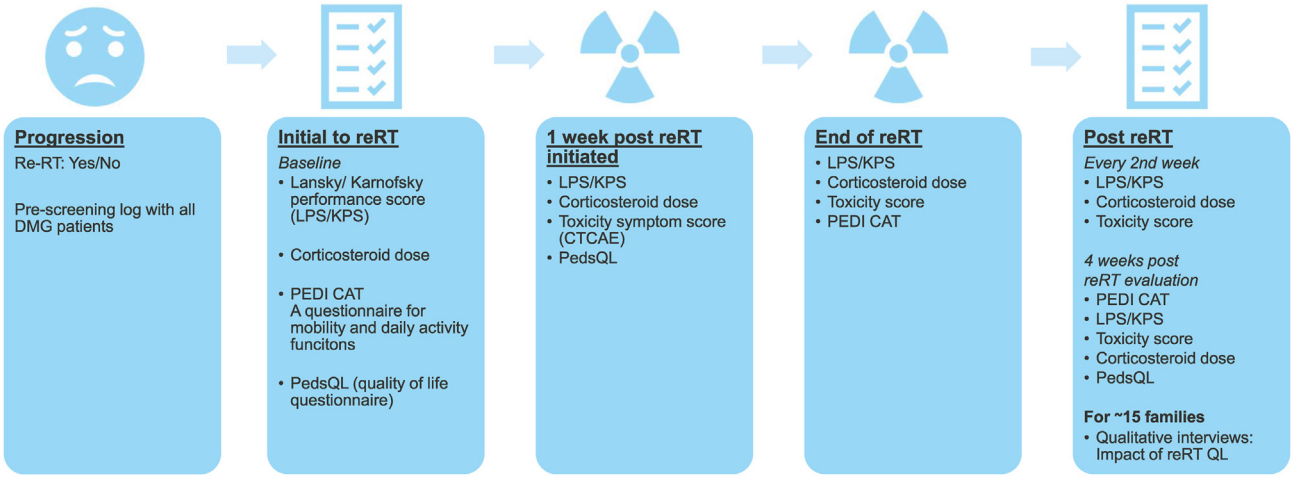

Fig 1. Visual flowchart of the REMIT protocol. REMIT, **Reirradiation of diffuse Midline glioma paTients.**

The PEDI score, originally published in 1992, has been revised as a computer adaptive test (CAT) [13,14]. PEDI-CAT measures functional domains such as daily activities and mobility. It is answered by proxy, either a family member (often parents) or the clinical staff. The PEDI-CAT will be performed upon referral to reirradiation, at end of reirradiation and 4 weeks later.

Corticosteroid Usage

Type and name of steroid used will be noted, as well as weight and height of the patient. The maximal daily dose since last consult will be reported, and whether this was regular medication or taken per necessity. Steroid dose levels will be reported at the start of reirradiation, during reirradiation, after reirradiation, and every second week until death. After 4 months, the dosage notation will be monthly.

Quality of Life Assessments

QOL will be assessed through two approaches: quantitative PedsQL scores and qualitative interviews. A PedsQL score will be collected with the PedsQL Cancer Module questionnaire before, during, and 4 weeks after last reirradiation fraction. The PEdsQL is validated in multiple languages and is designed as a modular instrument to measure QoL in children and adolescents aged 2−18 years [15]. The generic core module can be integrated with disease-specific modules such as the Cancer Module. It is either self-reported by the child or proxy-reported (often by the parent(s)). For a subgroup of patients, an interview approx. 4 weeks after reirradiation will be performed, initially this will be the Danish patients but, if possible, also other nationalities. The interviews will follow a semi-structured interview guide focused on the practical, emotional, and existential impact of reirradiation on the daily lives of the patients and their families. Data analysis will follow the methodology described by Malterud, and interviews will continue until saturation as defined by the methodology [16].

Flow-chart of the protocol is illustrated in Figure 1.

Other secondary objectives in REMIT are image-guided characterization of the anatomical site of progression compared to the primary lesion, and assessment of cumulated radiation dose to critical structures in the brain, brain stem, and spinal cord following reirradiation.

Hypothesis 3. Site of disease progression is predominately in-field and cumulative dose to the OARs during reirradiation is not associated with increased toxicity.

Endpoints will be radiotherapeutic parameters (dose volume histograms, cumulative doses in EQD2 reirradiation type (type 1, 2, or 3 [11])) correlated to toxicity grades (CTCAE).

Imaging and radiation treatment plans from the 1st and 2nd courses of radiotherapy will be collected and analyzed. Doses will be corrected for fraction-sized effects using Withers formula and subsequently added using deformable registration. Accumulated doses and toxicities will be reported as individual patient data.

REMIT also includes the following exploratory analyses:

- Delineation study

The delineation in tumor volume among the participating institutions will be compared and the variation described. This will improve the delineation-related uncertainty and, consequently, the applied margins (and hence irradiated volume) can be diminished. This will most likely lead to a more uniform treatment across institutions.

- The impact of reirradiation on the patients and their families

We plan to assess the value of reirradiation in terms of the practical, emotional, and existential impact on patients and their families. This will be done with a qualitative methodology as described above with semi-structured interviews with the parents of a subgroup of the included patients.

- Referral patterns

We believe there is a lack of knowledge on referral patterns of patients with progressive DMG to reirradiation, and the reasons for not offering reirradiation are underreported in the literature, suggesting selection bias or inequity in access to palliative treatments across institutions.

A prescreening log of all DMG patients at the involved institutions will be made. This will enable characterization and analysis of referral patterns of DMG patients to reirradiation.

Patients

Fifty-nine patients with radiologically and/or histologically verified DMG will be included in a two-stage design: Initially, 29 patients will be accrued, and an interim analysis done. If toxicity is below the predefined threshold, another 30 patients will be accrued in a second stage.

Inclusion criteria

- Age $\geq$12 months to $\leq$18 years at enrollment.
- At least 6 months have elapsed from the first day of the first radiotherapy course for DMG.
- First course of radiotherapy.
  - Arm A: 54Gy/30 fractions.
  - Arm B: Any other radiation dose and fractionation.
- Full recovery from all acute and subacute toxicities of the first radiotherapy course.
- Clinical and/or radiographic progression.
- Lansky Play Scale (for patients younger than 12 years) or Karnofsky performance status $\geq$50%.
- Life expectancy $>$12 weeks after start of reirradiation.
- Written informed consent according to local laws and regulations.

Exclusion criteria

- Presence of leptomeningeal spread or multifocal disease on MRI at progression.
- Other co-morbidities that, according to the treating physician, would impair participation in the study.
- >1 course of previous CNS/facial radiotherapy.
- Neurofibromatosis type 1.
- Inability to complete the follow-up of the study for, e.g. geographic, social, or mental reasons.

Patient Information

Patient and parents will receive written and oral information about the protocol and will be accrued at progression prior to the start of any new irradiation, chemotherapy, targeted drug therapy or surgery at the respective Departments of Pediatric Oncology or Radiotherapy.

Treatment Planning and Delivery

Reirradiation should be initiated no later than 4 weeks following clinical and/or radiological progression. Radiotherapy and chemotherapy/targeted drug therapy may be given concomitantly. The start of reirradiation should, however, not be delayed due to the start of a new chemotherapy or targeted drug therapy.

The dose prescription for reirradiation is 20Gy/10 fractions. There are no strictly defined dose constraints to the brain stem or other OARs. Magnetic resonance and computed tomography images must be coregistered prior to delineation and treatment planning, focusing on the treatment area. Radiotherapy can be delivered with external photon beam radiotherapy (either IMRT or VMAT) or using protons using RBE conversion 1.1.

Gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) will be determined according to ICRU50 and ICRU62 criteria.

- GTV will be delineated as a visible tumor as defined by the T2-weighted/FLAIR hyperintensity images on the MR scan and as seen on the planning CT.
- CTV is defined as the GTV + 0–5 mm margin depending on tumor volume adjusted to anatomical borders.
- PTV margin follows the institutional practice and is registered.

Safety

Patient safety and quality assurance procedures during radiotherapy are applied routinely in the clinic will be adhered to. As reirradiation is done according to institutional practice, it does not infer any extra risk for the patients. There will be particular focus on not inducing extra stress to the families participating in the qualitative interviews and additional follow-up will be offered to individual families, if needed.

Ethical Considerations

The REMIT protocol is a nonrandomized, prospective, biomedical feasibility study. The trial will be conducted according to the Declaration of Helsinki (Seoul version, October 2008). The trial has been reported to clinicaltrials.gov, the Danish Data Protections Agency and appropriate health authorities in Denmark, Norway, and Sweden.

Data Analysis

CTCAE grading, performance status, PEDI-CAT scores, and changes in steroid dose levels are surrogate markers for the potential clinical benefit, here addressed as palliative efficacy.

The patient cohort will be described using descriptive methods. Baseline characteristics include demographic data, gender, histological diagnosis, grade, genomic profile, age at diagnosis and reirradiation, and antineoplastic treatments. Categorical variables will be presented as frequencies and percentages. Continuous variables will be presented as medians with range and/or interquartile range and means with standard deviation if justified. The number of missing data will be specified for each variable.

Any variable with missing data will be handled with multiple imputations. If the patient dies within 4 weeks post-reirradiation this will be described.

Sample Size

Simon's optimal two-stage design has been used for sample size calculation [17]. The null hypothesis (H0) is that the probability of grade 4–5 reirradiation-related toxicity is too high (>15%) to continue the study. This will be tested against a one-sided alternative. The alternative hypothesis (H1) states the true rate of severe toxicity (grade 4–5) to be 5%. The trial is carried out in two stages. In stage I, a total number of 29 patients is accrued. If grade 4–5 toxicity for 4 patients or more is registered, the study will be stopped. Otherwise, an additional 30 patients will be accrued in stage II, resulting in a total sample size of 59. H0 will be rejected if 5 patients or less have grade 4–5 toxicity. The design controls the type I error rate at 10% and yields the power of 90%.

Collaborators

REMIT is a Nordic study, presented to and supported by the radiotherapy group of the Nordic Society of Paediatric Haematology and Oncology (NOPHO) and will open for accrual in Denmark, Sweden, and Norway in 2024. The protocol is open for more collaborators if interested.

Discussion

Reirradiation of progressive DMG has improved OS with approximately three to six months [7,18,19], but the studies

are mainly retrospective and prospective clinical trials of reirradiation are lacking [20]. Despite the reported survival benefit, a recent survey found that reirradiation was implemented to varying degrees [19]. Regardless of no consensus and an unaddressed risk of selection bias of patients, treatment with a second course of reirradiation is increasingly reported in case studies, with results suggesting survival benefit [21,22]. This emerging trend with a second course of reirradiation underlines the need for a clinical trial to systematically evaluate reirradiation.

Prospectively acquired knowledge of the palliative efficacy of reirradiation of DMG disease is limited and has only been reported by Amsbaugh [20]. Palliative treatments, such as reirradiation, should offer relief and be meaningful to the patients and their families. Studies have shown that bereaved parents are at risk for prolonged grief and psychologic distress after losing a child to cancer [23–28]. A study suggested a positive effect on parental long-term grief when the palliative treatment had a holistic approach to patients [29]. Amsbaugh *et al.* included QOL in their study using the PedsQL score. They showed that QOL improved after reirradiation for 64% of the patients, but there was a great variability among patients as well as different follow-up times, which makes the interpretation of QOL difficult. Even though QOL and the palliative efficacy are complex to evaluate; the insight is important and necessary for the physician and the families to make an informed choice about the offered palliative treatments – even for diseases with a minimal gain in OS. The REMIT protocol is designed to evaluate toxicity as well as assess performance status (LPS/KPS), activities of daily living (PEDI-CAT), supportive medicine (corticosteroid usage), and includes a qualitative analysis of the impact of reirradiation for the patients and their families (PedsQl questionnaire and qualitative interviews). This will address our current knowledge gap in reirradiation for DMG disease, beyond OS.

The risk of selection bias in previous studies in reirradiation of DMG have been raised, hence REMIT includes a prescreening log of DMG patients to address this. In a large North American survey distributed to 396 physicians, only 35% responded and, of these, 88% considered reirradiation as a treatment option [19]. This data suggests that the palliative approach to DMG varies significantly, and there might be inequity bias in the treatment options offered to patients.

In conclusion, reirradiation is a promising palliative treatment of DMG, but there is a need for systematic prospective studies as addressed by REMIT.

Ethics

The study has been approved by The Danish Ethical Committee (H-202321567 01.09.2023) and by The Danish Data Protection Agency (p-2023-14795) and by the Swedish Ethical committee (Dnr 2024-00111-01, 11.04.2024). The study has been registered at clinicaltrials.gov (NCT06093165). All eligible patients and their families will receive oral and written information about the study. Signed consent form is obligatory.

Author contribution

MVM is the principal investigator of this study and drafted the protocol design together with sub-investigator DEØ. MVM, DEØ, HM, AE, SL and RM are the local site-investigators. MVM, DEØ, HM, AE, SL, IRV, and RM contributed to the design of the protocol. AS, MK, KN and RM are the treating clinicians from the collaborating paediatric department at Copenhagen University Hospital and have contributed to the final manuscript. All authors have read, reviewed, and approved the final manuscript.

Data availability

No relevant.

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Conflict of interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Maja Maraldo reports financial support was provided by Danish Cancer Society. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

CTCAE	Common Terminology Criteria for Adverse Events
CT	Computed tomography
CTV	Clinical target volume
DMG	Diffuse midline glioma
F	fractions
GTV	Gross tumor volume
Gy	Gray
NOPHO	Nordic Society of Paediatric Haematology and Oncology
KPS	Karnofsky performance status
LPS	Lansky performance status
OARs	Organs at risk
PTV	Planning target volume
PedsQL	The Pediatric Quality of Life Inventory
PEDI-CAT	Paediatric Evaluation of Disability Inventory computer adaptive test
QOL	Quality of life
REMIT	Reirradiation of diffuse midline glioma patients
reRT	Reirradiation

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