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Optimal irradiation intervals in stereotactic radiotherapy for patients with brain metastases

Submission date
22/11/2022

Recruitment status
Recruiting

Registration date
23/11/2022

Overall study status
Ongoing

Last Edited
23/11/2022

Condition category
Cancer

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Radiobiological daily changes within tumors are considered to be quite different between stereotactic radiotherapy (SRT) (e.g., 50 Gy in 4 fractions) and conventional radiotherapy (e.g., 60 Gy in 30 fractions). Most tumors have hypoxic tumor cells which are radioresistant and can cause a recurrence after radiotherapy. During the period of daily irradiation, surviving hypoxic cells within tumor reoxygenate and get more sensitive to successive irradiation. From the data of radiobiological basic experiments, we consider that reoxygenation continues more than three days after single high-dose irradiation. We think that longer intervals more than 24-hour may be necessary to allow more reoxygenation to occur and enhance therapeutic efficacy of SRT. We aim to assess the optimal interval of irradiation in SRT and compare outcomes of daily irradiation with irradiation at two- to three-day intervals in SRT for patients with one to five brain metastases.

Who can participate?
Patients aged 20 or older with one to five brain metastases, less than 3.0 cm diameter, and Karnofsky Performance Status greater than or equal to 70.

What does the study involve?
A total of 70 eligible patients will be enrolled. After stratifying by the number of brain metastases (1, 2 vs. 3–5) and diameter of the largest tumor (<2 cm vs. ≥2 cm), we randomly assigned patients (1:1) to receive daily irradiation (Arm 1), or irradiation at two- to three-day intervals (Arm 2). Both arms are performed with total dose of 27-30 Gy in 3 fractions.

What are the possible benefits and risks of participating?
No particular benefit is expected from participating in this clinical trial. With regards to risks of participating, mini mental status examination (MMSE) needs to be evaluated every 6 months after SRT.

Where is the study run from?
Participating institutions will be six academic and four general hospitals in Japan. One of the

participating institutions is Nagoya City University Hospital (Japan), and the Principal Investigator, Dr Natsuo Tomita is based there. In each participating institution, the institutional review board will approve the protocol before patient enrollment occurred.

When is the study starting and how long is it expected to run for?
August 2022 to September 2028

Who is funding the study?
Hori Science and Arts Foundation (Japan)
Grant-in-aid for research on radiation oncology of JASTRO 2021-2022 (Japan)
Japan Society for the Promotion of Science (JSPS) KAKENHI

Who is the main contact?
Dr Natsuo Tomita, c051728@yahoo.co.jp

Contact information

Type(s)
Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
UMIN000048728

Study information

Scientific Title

Daily irradiation versus irradiation at two- to three-day intervals in stereotactic radiotherapy for patients with 1-5 brain metastases: a multicenter randomized phase II trial

Study objectives
Local control is superior in irradiation at two- to three-day intervals than in daily irradiation Iin stereotactic radiotherapy for patients with one to five brain metastases.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 02/08/2022, IRB of Nagoya City University Graduate School of Medical Sciences (Nagoya City University Hospital, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya, Aichi, 467-8601, Japan; no telephone number provided; irb_jimu@med.nagoya-cu.ac.jp), ref: 46-22-0004

Study design
Multicenter open-label randomized phase II trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
One to five brain metastases with less than 3.0 cm diameter.

Interventions
In stereotactic radiotherapy (SRT) of 27-30 Gy in three fractions for patients with one to five brain metastases with less than 3.0 cm diameter, daily irradiation is used in the standard arm while irradiation at two- to three-day intervals is performed in the experimental arm.
Both arms are performed daily with a total dose of 27-30 Gy in 3 fractions (9-10 Gy per fraction).
Arm 1 (standard arm): consecutive daily irradiation; total SRT duration, 3 days.
Arm 2 (experimental arm): irradiation at two- to three-day intervals; total SRT duration, 8 days.

The study will employ a 1:1 randomization between Arm 1 (consecutive daily irradiation) and Arm 2 (irradiation at two- to three-day intervals). Patients will be stratified by (1) maximum diameter (≤ 2 cm vs. > 2 cm) among their brain metastases and (2) number of brain metastases (1, 2 vs. 3-5). Random assignment of treatment groups is centrally managed using the web-based system of Mujinwari (Iruka System Ltd., Tokyo, Japan).

Intervention Type
Procedure/Surgery

Primary outcome(s)
Intracranial local control rate (IC-LC), defined as intracranial local control at initially treated sites at 12 months

Key secondary outcome(s))
1. Intracranial progression-free survival (IC-PFS), defined as intracranial PFS at initially treated and new sites at 12 months (and 6 and 24 months).

2. Overall survival (OS), defined as the time from the date of randomization to death from any cause at 12 months (and 6 and 24 months).
3. Toxicity, assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 at 12 months (and 3 and 24 months).
4. Non-worsening of Karnofsky performance status (KPS), defined as the time from randomization to decline of KPS from any cause.
5. Non-worsening of mini mental status examination (MMSE), defined as the time from randomization to decline of MMSE from any cause.

Completion date
01/09/2028

Eligibility

Key inclusion criteria
1. Age 20 years or older.
2. Karnofsky Performance Status (KPS) > or = 70.
3. Total number of 1-5 brain metastases by enhanced magnetic resonance imaging (MRI).
4. Brain metastases with less than 3.0 cm diameter by enhanced magnetic resonance imaging (MRI).
5. Willing to provide informed consent.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
20 years

Sex
All

Key exclusion criteria
1. Histological type of the primary site is lymphoma, small cell lung cancer, and germ cell tumor.
2. Metastases of the brainstem.
3. Meningeal carcinomatosis.
4. History of whole brain radiation therapy (WBRT) or substantial overlap with a previously treated radiation volume.
5. Surgical history for BM.
6. Difficult to be enrolled to the study by reason of insanity.
7. Inability to use enhancing agent for MRI due to low renal function or allergy.
8. In pregnancy or with expectation of pregnancy
9. Physician dismiss as subject of the study.

Date of first enrolment

01/09/2022

Date of final enrolment
31/03/2026

Locations

Countries of recruitment
Japan

Study participating centre
Nagoya City University Hospital
Japan
467-8601

Study participating centre
Kitasato University School of Medicine
Japan
252-0329

Study participating centre
Gifu University Hospital
Japan
501-1194

Study participating centre
Aichi Medical University
Japan
480-1195

Study participating centre
Nagoya City University East Medical Center
Japan
464-8547

Study participating centre
Nagoya City University West Medical Center
Japan
462-8508

Study participating centre
Ichinomiya Municipal Hospital
Japan
491-8558

Study participating centre
Okazaki City Hospital
Japan
444-8553

Study participating centre
Nagoya Ekisaikai Hospital
Japan
454-8502

Study participating centre
Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital
Japan
466-8650

Sponsor information

Organisation
Nagoya City University Hospital

ROR
https://ror.org/02adg5v98

Funder(s)

Funder type
Charity

Funder Name
Hori Science and Arts Foundation

Funder Name
Grant-in-aid for research on radiation oncology of JASTRO 2021-2022

Funder Name
Japan Society for the Promotion of Science (JSPS) KAKENHI

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from Natsuo Tomita (e-mail: c051728@yahoo.co.jp).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes