Reduced-dose Whole Brain Radiation Therapy Combined with Stereotactic Irradiation for Brain Metastases: Multi-institutional Phase II Study

Study type: Single-arm phase II clinical exploratory study

Study group

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Representative

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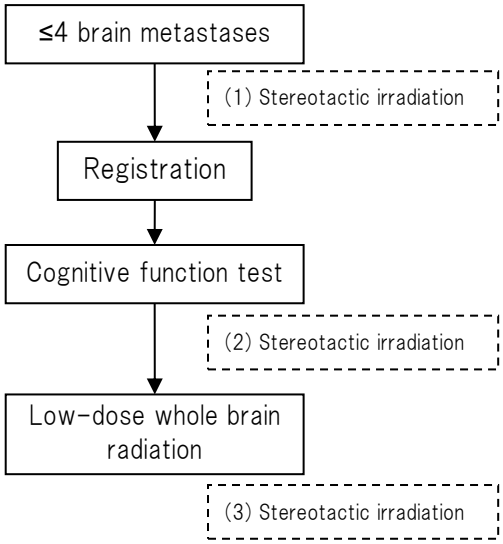
Schema



Stereotactic irradiation will be acceptable at any of timing (1), (2), and (3).

Observation and test schedule (the number of months will be counted from the completion of low-dose whole brain radiation)

Test timing / Item	Before treatment	After treatment (month)							
		4	6	8	9	12	18	24	Every 6M thereafter
MRI	○	○	○		○	○	○	○	○
Cognitive function test	○	○		○		○	○	○	○
QOL survey	○	○		○		○	○	○	○

(The tests will not be limited to those performed at the above timing. The acceptable range for the test timing is ±1 month.)

1. Objective and Hypothesis

1.1 Objective: To minimize late cognitive decline without increasing the intracranial tumor recurrence rate by optimizing whole brain dose fractionation pattern when whole brain radiation is combined with stereotactic irradiation in patients with no more than 4 brain metastases.

1.2 Hypothesis: Invisible micrometastases can be controlled by low-dose whole brain radiation (25 Gy/10 fractions) used in prophylactic whole brain radiation while visualized brain metastases are controlled by stereotactic irradiation. Combined use of whole brain radiation with stereotactic irradiation can be expected to yield an effect of improving the rate of local control of visible metastases. The use of this treatment strategy both reduces the high intracranial tumor recurrence rate that becomes a problem in stereotactic irradiation monotherapy and allows the reduction of the risk of cognitive function decline that causes a problem in long-term survivors after whole brain radiation.

2. Background and Rationale

2.1 Standard therapy for target disease and its problems

Brain metastases are considered to occur in approximately 10% to 40% of patients who die of cancer, and approximately 350 thousand people died of malignant neoplasm in Japan in 2010 (statistical table database of the Ministry of Health, Labour and Welfare). Therefore, annually 35 thousand to 140 thousand patients are calculated to be affected by brain metastases in Japan. The prognosis of brain metastases in their untreated natural history is not well understood. According to reports before use of CT and MRI had become common, the median survival time (MST) was considered to be 1 month without treatment, 2 months when steroids are used, and 3 to 6 months when whole brain radiation is performed. Recently, there have been many reports that MST after treatment is approximately 7 months, and long-term survival exceeding 2 years has sporadically been reported. This can be considered the results of the combined effects of: 1) early diagnosis owing to the prevalence of, and improvement in the quality of, MRI; 2) the prevalence of effective local treatment such as stereotactic irradiation; and 3) progress in systemic drug therapy, including molecular target drugs.[1]

Standard therapy for brain metastases, which are hematogenous metastases, is whole brain radiation. Recently in Japan, however, there has been an increasing number of institutions that have adopted a treatment policy in which only stereotactic irradiation is performed as the initial treatment without whole brain radiation in association with the prevalence of stereotactic irradiation devices. This trend is based on the reasoning that cognitive function decline, a late adverse reaction, can be avoided if whole brain radiation is not performed. There have been 3 reports of randomized studies comparing this stereotactic irradiation monotherapy and whole brain radiation + stereotactic irradiation combination therapy thus far, including JROSG99-1 conducted by our group.[2,3,4] These reports

have demonstrated that not performing whole brain radiation at the initial treatment does not cause any difference in survival time but significantly increases both the intracranial late recurrence rate and the local recurrence rate in lesions treated with stereotactic irradiation compared to cases in which combined therapy with whole brain radiation is performed (Table 1).

Table 1) Intracranial recurrence rate in 3 randomized studies

Study group	**Type of intracranial recurrence**	**SRS alone**	**SRS＋WBRT**	**P**
JROSG99-1 [2]	Local recurrence rate	28% (1-yr)	11% (1-yr)	0.002
	Intracranial late recurrence rate	64% (1-yr)	42% (1-yr)	0.003
MDACC [3]	Local recurrence rate	37% (1-yr)	0% (1-yr)	0.02
	Intracranial late recurrence rate	55% (1-yr)	27% (1-yr)	0.02
EORTC22952-26001 [4]	Local recurrence rate	31% (2-yr)	19% (2-yr)	<0.001
	Intracranial late recurrence rate	48% (2-yr)	33% (2-yr)	0.023

This high intracranial recurrence causes cognitive function decline in patients with brain metastases. In JROSG99-1, cognitive function before and after treatment was measured over time using MMSE, a simple battery of cognitive function tests. The results revealed that the cognitive function rate tends to be higher in the whole brain radiation combination group than in the stereotactic irradiation monotherapy group up to approximately 2 years after treatment. This trend has been speculated to be due to cognitive function decline caused by the high recurrence of brain metastases observed when whole brain radiation is not performed (Fig. 1).[5] Similar results have also been supported by other studies.[5,6] Therefore, it can be considered that omission of whole brain radiation lacks its basis in most patients with brain metastases in whom the median survival time is approximately 7 months.

Meanwhile, it is also true that cognitive function decline such as deterioration of memory among late adverse reactions due to whole brain radiation significantly decreases QOL particularly in long-term survivors. Such cognitive function decline is considered to be caused by irreversible degeneration of subcortical white matter. The condition progressively worsens once symptoms develop, and effective therapy has not been established. Therefore, if attention is paid to the QOL of long-term survivors who achieved intracranial control, it can be considered that whole brain radiation had better not be performed, which is opposed to the former idea.

When these things are comprehensively considered, both intracranial tumor control and late

adverse reactions to radiation are important factors influencing the preservation of cognitive function. Therefore, if the dose of whole brain radiation can be reduced to the level that does not cause a problem in late cognitive function and if it can be confirmed that the dose does not worsen the intracranial recurrence rate compared to conventional whole brain radiation, new standard dose fractionation in combined use with stereotactic irradiation may be established.

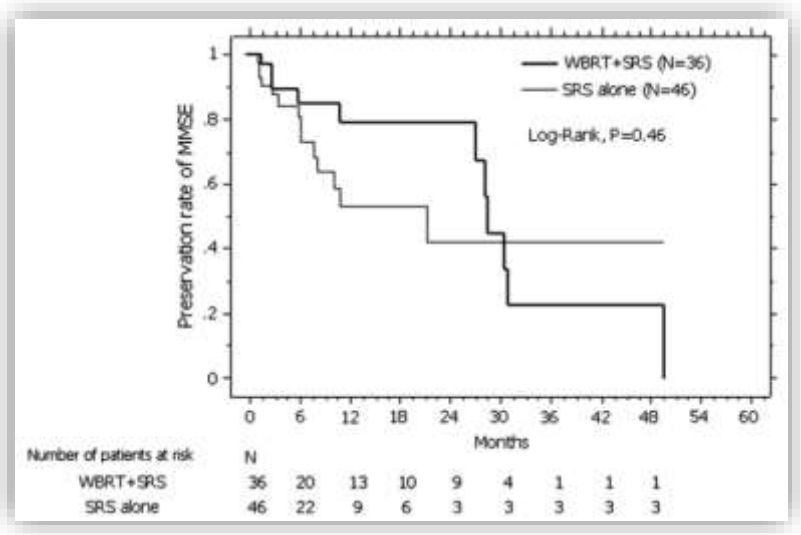


Fig. 1）JROSG99-1　cognitive function preservation rate [5]

2.2 Problems in dose used in whole brain radiation and measures against them

The therapeutic whole brain radiation normally used at present (30 Gy/10 fractions, 37.5 Gy/15 fractions) was established in the 1970s to 80s, which is before MRI and stereotactic irradiation had become common.[1] The life expectancy of patients with brain metastases was considered to be approximately 4 months back then even if systemic conditions were good and whole brain radiation was performed. However, because of early detection by the prevalence of MRI and the improvement of systemic therapy, the mean life expectancy has increased to approximately 7 months and reports of long-term survivors who survive for more than 2 years have begun to occur. As for adverse reactions due to whole brain radiation, early reactions such as headache and nausea are reversible and do not pose a serious clinical concern. Meanwhile, cognitive function decline such as deterioration of memory among late adverse reactions observed a half-year or more after radiation significantly decreases QOL particularly in long-term survivors. Such cognitive function decline is considered to be caused by irreversible degeneration of subcortical white matter. The condition progressively worsens once symptoms develop, and effective therapy has not been established. Therefore, there is an urgent need to establish a radiation schedule that takes into account the risk of late adverse reactions and that fits with present-day advances.

There are 2 types of whole brain radiation: “therapeutic” radiation, in which treatment is given in a state where the presence of brain metastases is already diagnosed as mentioned above, and “prophylactic” radiation. In “prophylactic” whole brain radiation, radiation is prophylactically performed in the whole brain when brain metastasis is not diagnosed using imaging but there is a high probability that brain micrometastases are present primarily in small cell lung cancer. As for the dose fractionation, patterns such as 30 Gy/15 fractions（3 weeks）[7, 8] and 25 Gy/10 fractions（2 weeks）[9] have been used. In a clinical study in which 356 patients with locally progressive non-small-cell lung cancer were randomized to the PCI (30 Gy/15 fractions) and follow-up groups（RTOG0214）, the cumulative brain metastasis onset rate after 1 year was significantly improved（p = 0.004）to 7.7% in the PCI group compared to 18% in the follow-up group.[7] However, recent memory and delayed playback among cognitive functions after 1 year tended to be low, though slightly, in the PCI group compared to the follow-up group. In a similar study conducted in Germany, the 5-year cumulative brain metastasis onset rate decreased from 27.2% to 9.1%, and no difference in the cognitive function decline rate has been reported between the PCI and follow-up groups.[8] In a single-arm study conducted using 25 Gy/10 fractions in patients with small cell lung cancer, transient decreases were observed in executive function and language after PCI, but they improved to pretreatment levels in the long term.[9] In view of these findings, 25 Gy/10 fractions was adopted in this study because the duration of radiation is as short as 2 weeks and because there is a possibility that cognitive function is preserved in long-term survivors.

3. Study Patients

3-1. Inclusion criteria

Patients who meet all of the following criteria 1) to 6) will be eligible.

1）Age: 20 to 80 years old

2）Systemic condition: Karnofsky Performance Status (KPS) of 70 or higher

3） Histopathologic diagnosis has been made based on extracranial lesions.

4）Patients with brain metastases for which stereotactic irradiation is indicated (4 or less brain metastases, maximum diameter 3.0 mm or lower)

5）Patients who consent to and cooperate with cognitive function tests and QOL surveys

6）Patients voluntarily provided written consent after receiving an adequate explanation and fully understood the content for participating in this study.

3-2. Exclusion criteria

Patients who meet any of the following criteria 1) to 6) will be excluded:

1）Have dysfunction or language disorder that interferes with tests.

2）Have a past history of whole brain radiation.

3）Have a past history of stereotactic irradiation in the brain (only 1 lesion), and control of the target lesion for at least 1 year has not been achieved based on imaging.
（PD patients after stereotactic irradiation: Exacerbation of at least 20% in long axis）

4）Have a past history of resection of brain metastases.

5） Have brain stem metastases.

6）The diagnosis of primary focus is small cell cancer, germ, or lymphoma.

7）Other cases where the investigator judges participation in the study is not appropriate

4. Study Participation Criteria for Sites Sites that meet either 1）or 2）

1）Both whole brain radiation and stereotactic irradiation can be performed.

2）Either whole brain radiation or stereotactic irradiation can be performed.

Examples of 2）

Example 1）Only stereotactic irradiation is performed at a site that belongs to the study group, and whole brain radiation is performed at a related site.

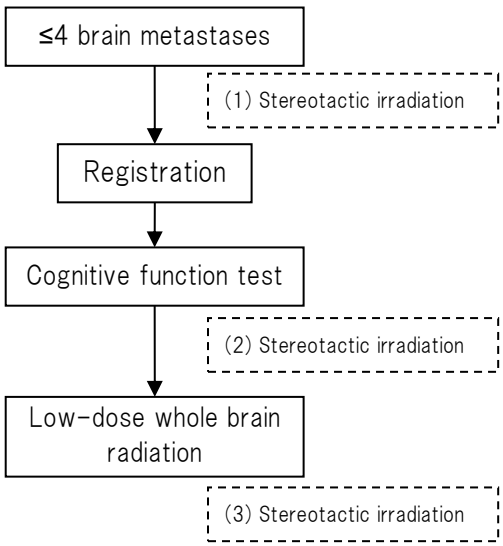
Example 2）Only whole brain radiation is performed at a site that belongs to the study group, and stereotactic irradiation is performed at a related site.

5. Study Methods

5-1. Study type and design

Phase II clinical study

5-2. Study outline



For the timing of stereotactic irradiation, there are plans to accept 3 patterns: (1) before registration, (2) between registration and whole brain radiation, and (3) after whole brain radiation.

Reasons）

(1) assumes the case where stereotactic irradiation is performed using a gamma knife. In the case a gamma knife is used, it is difficult to register patients before stereotactic irradiation because the number of metastases is determined by MRI at stereotactic irradiation.

(2) assumes the case where both stereotactic irradiation and whole brain radiation can be performed at the site.

(3) assumes the case where whole brain radiation is performed at a hospital at a business trip destination, etc. and stereotactic radiation is subsequently performed at a university hospital or cancer center.

5-3. Procedure for registration

Patients will be anonymized at each site at registration to protect their privacy. (A subject identification code will be assigned to each patient using a comparison table of anonymization number.)

1） Registration activities will be performed by the subinvestigator.

2） Eligibility at registration will be determined at the discretion of the subinvestigator, and it will be regularly verified by the study secretariat.

3） A registration application form in which necessary items are entered will be faxed to the study secretariat within 1 week after registration or a scanned PDF file will be sent to the study secretariat by e-mail within the same period.

4） The study secretariat will be established in the Department of Radiology, Niigata University Graduate School of Medical and Dental Sciences.

6. Radiation Therapy (Study Treatment, Concomitant and Supportive Therapy, Post-radiation Therapy)

6-1. Low-dose whole brain radiation 2.5 Gy x 10 times（total dose 25 Gy）. Isocenter prescribed.

6-2. Stereotactic irradiation

Prescribed points (isocenter, margin of GTV, or margin of PTV) will be consistent at each site.

In the case of stereotactic surgical irradiation, 2 cm or less, 22 to 25 Gy and 2 to 3 cm, 18 to 22 Gy will be the standard.

In the case of stereotactic radiation therapy, a dose fraction with a biological effect almost equal to the above will be used as a guide (e.g., 28 to 35 Gy/4 fractions).

*** Representation of prescribed doses of stereotactic irradiation**

GTV: The enhanced area on MRI

CTV: The same as GTV

PTV: 0, 1, or 2 mm. Used PTV-margin will be reported.

Reporting items

1. Definition of indicated point and dose at the point
2. D_{99}, D_{95}, Dmin, and Dmax of GTV
3. D_{99}, D_{95}, Dmin, and Dmax of PTV, and used PTV-margin

6-3. Rules on concomitant medication (therapies)

Any antitumor agents on the day of radiation will be prohibited in principle. If such use is revealed after the cognitive function tests following registration, the used drugs and dose will be specified, and follow-up investigations including the cognitive function tests and the imaging tests will be continued according to the study.

6-4. Criteria for discontinuation and dropout

（1）Discontinuation

If the following events occur during the study, administration of the study drug will be discontinued at the discretion of the investigator. Evaluations will be performed at discontinuation, and the timing of and reason for discontinuation, and comments will be specified in the investigation form.

1）Difficult to continue administration due to adverse events

2）Concomitant occurrence or worsening of serious complications or accidental symptoms

3）Request from the patient or patient's family members to discontinue the study

4）Continuation of the study is judged difficult by the investigator, etc.

（2）Dropout

Patients who stop visiting the hospital for their convenience will be considered as dropouts, and the reason for dropout will be clarified.

6-5. Post-radiation therapy

There will be no restrictions on post-radiation therapy for recurrence of brain metastasis. The description of treatment performed must be reported.

7. Evaluation and Reporting of Adverse Events

7-1. Definition of adverse event

An adverse event is defined as any unfavorable or unintended sign, symptom, or disease that occurs to a subject who received study treatment, whether or not considered related to the radiation therapy. Among adverse events, those corresponding to any of the following are defied as "serious adverse events." In this clinical study, adverse events observed within 90 days after the start of radiation are considered to be early adverse events, and those occurring

thereafter are regarded as late adverse events. “Serious adverse events” are as follows:

1）All deaths during protocol treatment or within 30 days after the last day of protocol treatment

2）Deaths after more than 30 days from the last treatment day for which a causal relationship to treatment cannot be ruled out

3）Unexpected Grade 4 central nervous toxicity

4）Central nervous toxicity that causes significant disability in the patient

7-2. Reportable adverse events

Reportable adverse events are defined as “serious adverse events” specified in 7-1.Definition of adverse events.

7-3. Procedure for reporting

Physicians who conduct the study will provide appropriate treatment if adverse events due to study treatment are observed during or after study treatment. If reportable adverse events occur, they will be immediately communicated to the coordinating investigator orally, or by phone, fax, or e-mail, whether or not they are related to study treatment. For serious adverse events (adverse reactions) for which a causal relationship to the study treatment or study drug cannot be ruled out (including unknown) by the investigator or principal investigator at the site, they will be immediately reported to the head of the medical institution and the coordinating investigator using a detailed document (“serious adverse event report”) to ask for their decision on the continuation of the study. The coordinating investigator will consult with safety evaluation committee members as necessary and notify each investigator as such.

8. Observation, Test, and Evaluation Items, and Schedule

8-1. Initial investigation items (specify items in the initial patient information form 1 to 3)

Overall items

1）Age

2）Sex

3) Handedness

4) Systemic condition: KPS

5）Primary organ, tissue type

6) Status of primary focus: Controlled (no progression for 6 months or longer), uncontrolled

7) Extracranial metastasis: Absent, present (in the case of present, controlled or uncontrolled)

8) History of chemotherapy: Absent, present (in the case of present, type)

9) Surgical history: Absent, present (in the case of present, specifics)

Items related to brain metastasis and its treatment

1) Number of metastases

2) Cerebral edema: Absent, present (in the case of present, less than 1/2 of hemisphere or at least 1/2 of hemisphere)

3) Symptoms associated with brain metastases (circle corresponding grades in the table)

4) Sites of brain metastases and diameter in 3 directions: Enter characteristics (solid, cystic) and diameter by site.

5) Drug use: Enter use of steroids, anticonvulsants, and opioids.

6) Radiation therapy: Whole brain dose and duration of treatment, and detailed information on stereotactic irradiation

Items related to cognitive function tests

1) Acoustic language learning test: Hopkins Verbal Learning Test-Revised, Japanese Edition （HVLT-R）

2) Executive function test: TMT (Trail-Making Test) attention (test A), executive function （test B）

3) Meaning fluency test: COWA (Controlled Oral Word Association) version 1（vegetables) and 2（animals）

4) EORTC QLQ30, BN20

- Versions of HVLT-R and COWA

To minimize the effects of learning effect and difference in versions on the analysis results, the versions of HVLT-R and COWA initially performed in each patient will be those assigned to each subject identification code in the comparison table of anonymization number. From the second test, the initial version + 1 (2 if the initial version is 1) will be used for HVLT-R, and another version (2 if the initial version is 1) will be used for COWA.

8-2. Follow-up investigation items (specify items in the follow-up patient information form 1 to 2)

1) Subject identification code

2) Date of consultation

3) Time from the completion of whole brain radiation

4) Date of brain MRI

5) Date of cognitive function tests and QOL survey

Overall items

1) Systemic condition: KPS; in the case of death, classify into neurogenic and non-neurogenic deaths

2) Drug use: Steroids, anticonvulsants, and opioids

3) Status of extracranial lesions

Items related to brain metastasis and its treatment

1) Size of sites to which stereotactic irradiation is performed, controlled or uncontrolled, and additional treatment

2) Presence or absence of new intracranial metastasis and rescue treatment

3) Meningeal dissemination

4) Status of cerebral edema

5) Symptoms associated with brain metastases

6) Adverse reactions associated with radiation therapy (ender grades based on CTCAE)

Items related to cognitive function tests

1) Acoustic language learning test: Hopkins Verbal Learning Test-Revised, Japanese Edition（HTLV-R）

2) Executive function test: TMT (Trail-Making Test) attention (test A), executive function（test B）

3) Meaning fluency test: COWA (Controlled Oral Word Association) version 1（vegetables) and 2（animals）

4) EORTC QLQ30, BN20

8-3. Observation and test schedule (the number of months will be counted from the completion of low-dose whole brain radiation)

Test timing / Item	Before treatment	After treatment (month)							
		4	6	8	9	12	18	24	Every 6M thereafter
MRI	○	○	○		○	○	○	○	○
Cognitive function test	○	○		○		○	○	○	○
QOL survey	○	○		○		○	○	○	○

(The tests will not be limited to those performed at the above timing. The acceptable range for the test timing is ±1 month.)

9. Target Sample Size and Study Period

9-1. Target sample size

70 patients (25 patients at Niigata University, 70 patients in the entire study)

[Rationale for target sample size]

The target sample size was established as 70 patients, including 8 ineligible and dropout

patients, to use the same number of patients as the 62 registered patients in the whole brain radiation (30 Gy/10 fractions) + stereotactic irradiation combination group in JROSG99-1 to confirm that intracranial the tumor recurrence rate is not significantly lower than that after normal-dose whole brain radiation in JROSG99-1 and to calculate the estimated intracranial tumor recurrence rate required at the launch of a phase III randomized study (low-dose whole brain radiation vs. normal-dose whole brain radiation) scheduled after the completion of this study (to be discussed with Professor Akazawa, Medical Statistics).

9-2. Study period

Registration period: 4 years (April 2012 to March 2016)

Study period: 5 years (April 2012 to March 2017), including the observation period

10. Endpoints

10-1. Primary endpoint

New intracranial metastasis rate at 6 months

10-2. Secondary endpoints

1) Rate of cognitive functional change at 4 months
2) Rate of cognitive functional change at 8 and 12 months
3) Local control rate at sites at which stereotactic irradiation is performed
4) Overall survival rate
5) Cause of death

10-3. Safety endpoint

All adverse events

11. Statistical Discussion

11-1. Definition of analysis set

Patients in whom study treatment is started among all eligible patients who meet the eligibility criteria will be included in the primary analysis set.

11-2. Interim analyses

The first interim analysis will be performed at the time the number of patients in whom at least 4 months have passed after treatment exceeds 10. An additional analysis will be performed every time 10 such patients are additionally reported thereafter. Intracranial control rate after low-dose whole brain radiation will be evaluated to deliberate the continuation of the study.

11-3. Statistical analysis manager

Kohei Akazawa, Professor, Department of Medical Information, Niigata University Medical & Dental Hospital

12. Preparation and Submission of Case Report Form

Deadline of submission

(1) Registration: Application form: At registration

(2) Initial patient information form: Within 2 weeks after the completion of treatment

(3) Follow-up patient information form and copies of cognitive function tests and QOL survey forms: Within 2 weeks after the completion of each consultation

13. Ethical Matters

13－1. Consideration for the human rights of subjects and methods for the protection of private information

All persons in charge of the study will conduct the study in compliance with the "Declaration of Helsinki (modified in October 2008)" and "Ethical Guidelines for Clinical Studies (revised on July 31, 2008, hereinafter referred to as the clinical study ethical guidelines)."

"In the handling of samples, etc. related to study conduct, they should be controlled by assigning numbers (subject identification codes) irrelevant of subjects' private information to give full consideration to the protection of subjects' privacy. A linkable 'comparison table of anonymized numbers' should be prepared for each participating site, and the principal investigator at each site should manage the table. The study secretariat should prepare 'patient registration forms' to manage patient information using subject identification codes. These numbers should be used when test results, etc. are sent to related sites such as the study secretariat, and adequate consideration should be given not to leak subjects' private information outside the hospital. When study results are published, they should be confirmed so that information based on which subjects can be identified is not included. Subjects' samples, etc. obtained through the study should not be used for non-research purposes."

13-2. Method for obtaining consent

The principal investigator will prepare the informed consent form and revise it as necessary. The prepared or revised informed consent form should be approved by the ethics committee.

The principal investigator or subinvestigator will give an adequate explanation to the subject using the informed consent approved by the ethics committee and obtain voluntary written consent for participation in the study from the subject himself/herself. The informed consent form must include at least the following:

1）That the study involves research.

2）The purpose of the study.

3）The method of the study.

4）The scheduled period of the subject's study participation.

5）The number of subjects scheduled to participate in the study.

6）Anticipated clinical benefits and risks or inconvenience.

7）If a patient is included as a subject, availability of alternative treatment to the patient, and important benefits and risks anticipated for the treatment.

8）Compensation and treatment available to the subject in the event of study-related injury.

9）That the subject's participation in the study is voluntary and that the subject or the subject's proxy consenter may refuse to participate or withdraw from the study at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

10）That the subject or the subject's proxy consenter will be immediately informed if information becomes available that may be relevant to the subject's or the proxy consenter's willingness to continue participation in the study.

11）Conditions or reasons for discontinuing participation in the study.

12）That the monitors, auditors, ethics committee, and regulatory authorities will be granted access to the original medical records without violating the confidentiality of the subject. And that, by affixing their name and seal, or signing a consent form, the subject or the subject's proxy consenter is authorizing such access.

13）If the results of the study are published, the subject's privacy will be protected.

14）The description of expenses to the subject, if any.

15）The description of payment to the subject, if any.

16）The name, title, and contact information of the principal investigator or subinvestigator

17）Who to contact at the participating medical institution for further information regarding the study and the rights of study subjects, or in the event of study-related injury.

18）What the subject should comply with.

A physician who gave an explanation and a person to be the subject or a person to be the proxy consenter will each date, and affix their name and seal on, or sign, the consent form upon fully understanding the written information. The consent form specifies that the subject or proxy consenter agrees to participate in the study. The principal investigator, etc. will give the subject a copy of the consent form with the names and seals, or signatures of the principal investigator, etc. and the person to be the subject.

14. Costs and Compensation

14-1. **Costs of treatment and burden of patients:**

Radiation therapies used in the study (whole brain radiation and stereotactic irradiation) are both covered by health insurance, and the treatment in the study can be performed as health insurance treatment. Therefore, medical costs, including test fees, during the study will be paid using insurance

and as the patient's out-of-pocket expenses. Study participants will thus pay an amount equal to out-of-pocket expenses in routine health insurance treatment. No costs will be charged for cognitive function tests.

14-2. **Compensation for the injury of patients**

This clinical study will be conducted using radiation therapies that are already covered by health insurance within the scope of their indications. Treatment of injury will be performed using the subject's health insurance as is the case with normal practice. No special compensation will be prepared for the study.

15. Approval of Institutional Review Board for Drugs and Medical Devices (IRB)

15-1. Approval of protocol, etc.

This study will be conducted after documents such as the protocol and informed consent form are reviewed and approved by the ethics committee or equivalent review board at the participating site.

15-2. Changes in the contents of the protocol, etc.

Category of changes in the protocol

Changes in the contents of the protocol after approval of the review board will be handled by classifying them into 2 types, amendment and revision.

The definitions and handling will be as follows:

① Amendment: A partial change in the protocol that may increase the risks of patients participating in the study or that is related to the primary endpoint of the study. Review and approval by the review board are required. The date of approval will be specified on the cover page.

② Revision: A change in the protocol that does not potentially increase the risks of patients participating in the study and that is not related to the primary endpoint of the study. Approval by the study representative is required. As for review and approval by the review board, the rules of the review board will be followed. The date of approval by the study representative will be specified on the cover page.

16. Discontinuation, Suspension, and Completion of Study

16-1. Discontinuation and suspension

In principle, the study will be continued until the number of registered subjects reaches the target sample size and evaluations are completed for all subjects. However, if unanticipated serious adverse reactions and obvious treatment-related deaths occur, there will be discussions about whether or not to continue the study.

1）When subject enrollment is difficult and it is judged very difficult to reach the planned

sample size.

2）When the objective of the study is achieved before the planned sample size is reached or the planned period elapses.

3） When the review board gives directions to change the protocol, etc. and it is judged difficult to accept the directions.

If discontinuation is recommended or directed by the review board, the study manager will discontinue the study. If discontinuation or suspension of the study is determined, it will be immediately reported to the hospital director as such in writing along with the reason.

16-2. Completion of study

At the completion of the study, the study manager will immediately submit a study completion report to the hospital director.

17. Case Handling

The coordinating investigator will consider the handling of subjects such as those who violated the study rules, those who discontinued the study, and dropouts before analyses following the completion of investigation, in view of recommendations by evaluation committee members on efficacy and safety.

18. Emergency Actions

Appropriate actions should be taken if serious adverse events, and serious complications or accidental symptoms are observed during the study.

19. Study Organization

19－1. Secretariat and data center

Department of Radiology, Niigata University Graduate School of Medical and Dental Sciences
Physician in charge: Kensuke Tanaka, Secretaries in charge:
Yukiko Morita, Mika Hasegawa
Tel: 025-227-2315（Office of the Department of Radiology）
FAX: 025-227-0788
E-mail: ktanaka510218@gmail.com
Study administrator: Hidefumi Aoyama
E-mail: h-aoyama@med.niigata-u.ac.jp

19-2. Protocol Data-Monitoring Committee

Chairman: Yasuo Saijo, Professor, Department of Oncology Medicine, Niigata University Medical& Dental Hospital

Member: Nobuhiko Yoshimura, Associate Professor, Division of Radiodiagnosis Department of Radiology, Niigata University Medical & Dental Hospital

Member: Yuichiro Yoneoka, Assistant Professor, Department of Neurosurgery, Niigata University Medical & Dental Hospital

19-3. Study participating sites

Sites will be recruited after approval of protocol concept. Approval of the institutional review board (IRB) of each organization is required for participation in the study. The representative of participating site can register subjects after notifying the date of IRB approval to the secretariat.

19-4. Statistical analysis manager

Kohei Akazawa, Professor, Department of Medical Information, Niigata University Medical & Dental Hospital

20. Publication of Study Results

The results of the study will be reported as a published article.

21. Study Funds and Conflict of Interest

This study will be conducted using the following study funds of the department that the study manager belongs to:

1）Niigata University Clinical Study Support Project, 2011 to 2014, total aid of 19 million yen (planned).

Study manager: Hidefumi Aoyama

Conflict of interest: None
Loss of the rights or benefits of subjects due to study conduct: None

22. Contact Information

① Eligibility criteria and matters requiring clinical judgment: Study secretariat

② Registration procedure, completion of case report form (CRF), etc.: Study secretariat

③ Adverse event reporting: Data-monitoring committee (established in Niigata University)

23. References

1. Abe E and Aoyama H. The Role of Whole Brain Radiation Therapy for the Management of Brain Metastases in the Era of Stereotactic Radiosurgery. Curr Oncol Rep. 2012; 14: 79-84

2. Aoyama H, Shirato H, Tago M, et al., Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA,* 2006. 295: 2483-2491.

3. Chang, E.L., Wefel JS, Hess KR, et al., *Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol*, 2009. 10: 1037-44

4. Kocher, M., Soffietti R, Abacioglu U, et al., Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol*. 2011; 29: 134-141.

5. Aoyama, H., Tago M, Kato N, et al., *Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. Int J Radiat Oncol Biol Phys,* 2007. 68: 1388-1395.

6. Li J, Bentzen SM, Renschler M, Mehta MP. Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function. *J Clin Oncol.* 2007; 25: 1260-1266.

7. Gore EM, Bae K, Wong SJ, et al. Phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small-cell lung cancer: primary analysis of radiation therapy oncology group study RTOG 0214. *J Clin Oncol.* 2011; 29: 272-278

8. Pottgen C, Eberhardt W, Grannass A, et al. Prophylactic cranial irradiation in operable stage IIIA non small-cell lung cancer treated with neoadjuvant chemoradiotherapy: results from a German multicenter randomized trial. *J Clin Oncol.* Nov 1 2007; 25: 4987-4992

9. Grosshans DR, Meyers CA, Allen PK, Davenport SD, Komaki R. Neurocognitive function in patients with small cell lung cancer: effect of prophylactic cranial irradiation. *Cancer.* 2008; 112: 589-595