TRIAL PROTOCOL

Photon Radiation Therapy for Multiple Brain Metastases: A Pilot Prospective Randomized Phase II Trial Comparing Standard Fractionation (30 Gy in 10 fractions) versus Hypofractionation (26 Gy in 4 fractions)

Trial registration: 993328

Affiliations: P.A. Hertsen Moscow Oncology Research Center Branch of FSBI NMRRC of the Ministry of Health of Russia, Russian Federation, Moscow city, 2nd Botkinsky Pr-d, 3, 125284

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Background

Optimal radiotherapy regimen for patients with multiple brain metastases (≥5 lesions) who are not candidates for stereotactic radiosurgery remains uncertain.

Objective

Comparison of the efficacy and toxicity of two whole-brain radiotherapy schedules in adult patients with multiple brain metastases.

Design

Single-center, pilot, prospective, randomized phase II trial.

Methods

50 patients will be randomized (envelope method) into: Group I (n=25) – standard fractionation (30 Gy in 10 fractions); Group II (n=25) – hypofractionation (26 Gy in 4 fractions).

Endpoints: local control, overall survival, quality of life (KPS, ECOG), neurological status (NANO), toxicity (RTOG, EORTC, CTCAE v5.0).

Expected results

Improved local control and quality of life in the hypofractionation arm without increased toxicity.

Keywords: brain metastases, whole-brain radiotherapy, hypofractionation, prospective randomized trial

Introduction

Brain metastases occur in 20–40% of cancer patients. Multiple lesions (≥5) are associated with poor prognosis and require optimized radiotherapy. When stereotactic radiosurgery is not indicated (e.g., high lesion burden, proximity to critical structures), whole-brain radiotherapy remains the standard. However, the optimal fractionation schedule is not established. Hypofractionation may shorten treatment time and offer radiobiological advantages due to higher dose per fraction. This trial compares standard fractionation (30 Gy/10 fractions) versus hypofractionation (26 Gy/4 fractions).

Methods

Study design

Single-center, pilot, prospective, randomized phase II trial. Approved by the Ethics Committee of the P.A. Hertsen Moscow Oncology Research Institute – branch of

the National Medical Research Center of Radiology, Ministry of Health of the Russian Federation.

Participants

Inclusion criteria:

- Multiple brain metastases (≥5 lesions, or fewer if stereotactic radiosurgery is not indicated)
- Age >18 years
- Morphologically verified primary tumor (for unknown primary, verification of metastatic lesion required)
- Signed informed consent
- Karnofsky Performance Status ≥60%
- Any life expectancy (any GPA score)
- No contraindications to external-beam radiotherapy

Exclusion criteria:

- prior brain radiotherapy
- severe somatic condition
- pregnancy
- psychiatric disorders.

Randomization

Envelope method at the time of CT simulation (open-label trial).

Radiotherapy planning and delivery

Immobilization:

Custom thermoplastic mask, supine position with standard headrest.

Simulation and planning:

CT of the brain (1 mm slice thickness, ≤1 mm spacing) co-registered with contrast-enhanced T1-weighted MRI (1 mm slice thickness). Planning systems: Monaco v5.51.10 (Elekta) and Eclipse v16.0 (Varian).

Target volumes:

GTV = gross tumor volume; CTV = whole brain down to C1 (including meninges if involved). PTV = CTV + 3 mm. Organs at risk: brain, globes, lenses, brainstem, cochleae, optic chiasm, optic nerves, spinal cord.

Dosimetry:

Monte Carlo algorithm; 3D-CRT or IMRT/VMAT. PTV coverage 95–107% of prescribed dose. Dose constraints (QUANTEC, $\alpha/\beta=3$ for brain, nerves): brain Dmax <60 Gy, brainstem Dmax <54 Gy, optic chiasm/nerves Dmax <55 Gy, cochlea Dmean <45 Gy, spinal cord Dmax <50 Gy.

Treatment delivery:

Linear accelerators (Elekta Versa HD, Infinity, Axesse; Varian Halcyon). Photon energy 6–10 MV. IGRT: XVI (Elekta) or CBCT (Varian). IGRT performed every fraction in the hypofractionated group and every other fraction in the standard fractionation group.

Concomitant medication

Dexamethasone 4–24 mg/day individually.

Assessments

Primary endpoint: Local control at 2 months (MRI assessment).

Secondary endpoints: Overall survival, quality of life, neurological status (NANO), toxicity (CTCAE v5.0), GPA and RPA scores.

Sample size and statistical analysis

25 patients per arm (total N=50). Statistical software: SPSS v26.0. Tests: Student's t, Mann-Whitney U, chi-square, log-rank test. Cox regression for multivariable analysis.

Ethics and informed consent

Approved by the Ethics Committee of the P.A. Hertsen Moscow Oncology Research Institute – branch of the National Medical Research Center of Radiology, Ministry of Health of the Russian Federation. All patients provide written informed consent.

Funding

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Statistical analysis

Statistical analysis was performed using GraphPad Prism 10.4.2.

The choice of statistical method depended on whether the quantitative data followed a normal distribution.

Descriptive Statistics:

Normally distributed quantitative data: Described using the mean (M) and standard deviation (SD), along with a 95% confidence interval (95% CI).

Non-normally distributed quantitative data: Described using the median, along with the lower and upper quartiles (Q1 and Q3) or a 95% confidence interval (95% CI).

Categorical data: Described using absolute values (n) and percentages (%).

Methods for Comparing Groups and Assessing Changes:

Student's t-test: Used for comparing two groups (including pairwise comparisons within one group over time) when the quantitative indicator had a normal distribution.

Wilcoxon signed-rank test: Used for pairwise comparisons (e.g., before and after treatment within the same group) when the quantitative indicator did not follow a normal distribution.

Mann-Whitney U test: Used for comparing two independent groups when the quantitative indicator did not follow a normal distribution. This non-parametric test compares the medians of the two groups.

Survival Analysis:

Kaplan-Meier method: Used to assess and plot patient survival functions. This method was chosen because it allows for the analysis of censored data, meaning it accounts for patients who may drop out of the study or have different follow-up times.

Significance Level:

Results were considered statistically significant if the p-value was less than 0.05 ($p < 0.05$).

Conflict of interest

The authors declare no conflict of interest.