

0 vs 2 mm Margins in Frameless Stereotactic Radiosurgery for Intact Brain Metastases: Study Protocol for a Randomized Trial

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Background

Frameless LINAC-based stereotactic radiosurgery (SRS) has become an increasingly utilized treatment for brain metastases. The clinical relevance of potential inaccuracies in localization with frameless SRS remains controversial. In frame-based SRS systems, the prescription dose is delivered to the gross tumor volume (GTV), delineated on a fine-cut post-contrast T1-weighted MRI, without a margin. When employing frameless systems, however, many centers will account for set-up uncertainties by adding a circumferential margin of 1-3 mm around the GTV to create a planning target volume (PTV). This PTV expansion ensures adequate tumor coverage if target motion occurs, but exposes more normal brain tissue to radiation and may increase the risk of adverse events. Given the paucity of data examining margin extent and the potentially significant consequences for treatment efficacy and morbidity, we propose a randomized prospective clinical trial evaluating 0 vs 2 mm marginal GTV to PTV expansions for treating patients with intact brain metastases with frameless SRS (clinicaltrials.gov NCT02747303).

Hypotheses

1. We hypothesize that frameless LINAC-based SRS with 0 mm PTV margins will be non-inferior to 2 mm margins with regard to local progression-free survival (PFS).
2. We also hypothesize that rates of clinically significant adverse events, including radionecrosis, will be increased in the arm with 2 mm margins.

Methods

Eligible patients will have histologically confirmed systemic malignancy, an ECOG performance status of 0-2, a life expectancy of >3 months, and a fine-cut gadolinium contrast-enhanced MRI demonstrating 1-5 parenchymal brain metastases, none exceeding 3 cm in maximum diameter. Patients who previously received cranial radiation will be excluded. After stratification by Diagnosis Specific Graded Prognostic Assessment, maximum GTV diameter, and treating institution, patients will be randomized to frameless SRS using the ExacTrac/Novalis system with either 0 or 2 mm GTV to PTV marginal expansions. The SRS dose will be 20 Gy or 18 Gy, prescribed to the highest isodose surface encompassing 99-100% of the PTV, for brain metastases with maximum GTV diameters of ≤ 2 cm or >2 cm, respectively. The primary endpoint is time to the earlier of either local failure or death after SRS (local PFS), and the secondary endpoint is the time to diagnosis of radionecrosis or pseudoprogression. This study aims to accrue 166 patients and is powered to demonstrate non-inferiority of the experimental arm for the primary endpoint with 80% power and a type I error rate of 5% using a one-sided test and a pre-defined non-inferiority hazard ratio of 1.5. It is also powered to detect the superiority of the experimental arm for the secondary endpoint with 80% power and a type I error rate of 5% using a two-sided test and a pre-defined superiority hazard ratio of 0.8.

Discussion

This study of frameless SRS technique will determine the impact of marginal PTV expansions on the clinical outcomes of primary interest: local PFS and radionecrosis.