**Clinical Investigation**

**Linear accelerator-based single-fraction stereotactic radiosurgery versus hypofractionated stereotactic radiotherapy for intact and resected brain metastases up to 3 cm: A multi-institutional retrospective analysis**

Brett H. Diamond, MD², Vikram Jairam, MD², Shaharyar Zuberi, BS³, Jessie Y. Li, BS², Timothy J. Marquis, MD⁴, Charles E. Rutter, MD³⁵ and Henry S. Park, MD, MPH²

¹Tufts University School of Medicine, Department of Radiation Oncology, Boston, MA 02111, USA
²Yale School of Medicine, Department of Therapeutic Radiology, New Haven, CT 06511, USA
³University of Connecticut School of Medicine, Department of Radiation Oncology, Farmington, CT 06032, USA
⁴Yale School of Medicine, Department of Medicine, New Haven, CT 06511, USA
⁵Hartford HealthCare, Department of Radiation Oncology, Hartford, CT 06106, USA

Correspondence to: Henry S. Park, MD, MPH, Department of Therapeutic Radiology, Yale School of Medicine, 35 Park Street, LL513, New Haven, CT 06511, USA. Email: henry.park@yale.edu; Phone: +1 (203) 200-2659; Fax: +1 (203) 785-4622

(Received: August 21, 2020; Accepted: November 24, 2020)

**ABSTRACT**

**Introduction:** Single-fraction stereotactic radiosurgery (SF-SRS) is typically used to provide local control of brain metastases. Recently, hypofractionated stereotactic radiotherapy (HF-SRT) has been utilized for large brain metastases. Data comparing these two modalities are limited for brain metastases ≤3 cm.

**Methods:** Patients with brain metastases receiving linear accelerator-based SF-SRS or HF-SRT were identified at three institutions. Local progression-free survival (LPFS), intracranial progression-free survival (ICPFS), overall survival (OS), and radionecrosis-free survival (RNFS) were determined from time of treatment.

**Results:** 108 patients (76 intact, 32 resected) with 184 brain metastases (142 intact, 42 resected) were included. There were no significant differences between SF-SRS and HF-SRT for intact metastases in 1-year LPFS (62.8% vs. 58.5%, p=0.631), ICPFS (56.9% vs. 55.3%, p=0.300), and OS (71.6% vs. 70.6%, p=0.096), or for resected metastases in 1-year LPFS (67.3% vs. 57.8%, p=0.288), ICPFS (64.8% vs. 57%, p=0.291), and OS (64.8% vs. 66.1%, p=0.603). There were also no significant differences in 1-year RNFS between SF-SRS and HF-SRT (92% vs. 92%, p=0.325).

**Conclusions:** There were no significant differences in LPFS, ICPFS, OS, and RNFS between SF-SRS and HF-SRT for brain metastases ≤3 cm suggesting SF-SRS may be preferred due to similar outcomes and reduced number of fractions.

**Keywords:** Stereotactic radiosurgery, hypofractionated stereotactic radiosurgery, hypofractionated radiosurgery, brain metastases, SRS, radiosurgery
INTRODUCTION

Brain metastases are a significant cause of morbidity and mortality for 20% of patients with cancer.\textsuperscript{1} For patients with brain metastases, the mainstays of treatment are radiation, surgery, and pharmacotherapy using targeted agents, immunotherapy, and/or chemotherapy. Since the advent of single-fraction stereotactic radiosurgery (SF-SRS), radiation has become increasingly used to provide local control of intracranial metastatic disease.\textsuperscript{2} SF-SRS offers advantages over whole brain radiotherapy by limiting neurotoxicity and providing similar long-term survival to both intact and resected brain metastases.\textsuperscript{3-5}

More recently, hypofractionated stereotactic radiotherapy (HF-SRT) has been used for the treatment of brain metastases that are large or high-risk in order to minimize toxicity.\textsuperscript{6,7} HF-SRT is similar to SF-SRS in that it is highly conformal stereotactic radiation; however, it is delivered over 2-5 fractions. HF-SRT offers theoretical radiobiological benefits as well as a similar safety and efficacy profile to SF-SRS when used to treat intact brain metastases.\textsuperscript{6,8,9} Similarly, other case series have suggested adequate control and improved safety profile of post-operative HF-SRT to resected brain metastases.\textsuperscript{5,7,10,11} However, little data exists comparing these treatment modalities for brain metastases up to 3 cm in size. We sought to carry out a multi-institutional retrospective analysis comparing outcomes following linear accelerator-based SF-SRS and HF-SRT for the treatment of brain metastases up to 3 cm, with the unique advantage of stratifying by delivery to intact versus resected tumors.

MATERIALS AND METHODS

This retrospective database study was approved by the institutional review boards of Yale School of Medicine, UConn Health, and Hartford HealthCare. A total of 108 consecutive patients with 184 total brain metastases diagnosed between 2010-19 were included in the study according to the following inclusion and exclusion criteria:

**Inclusion Criteria**

- Age ≥ 18 with histologically proven solid cancer with brain metastases diagnosed by brain magnetic resonance imaging (MRI)
- Patients treated with linear accelerator-based SF-SRS or HF-SRT
- Brain metastases ≤ 3 cm in diameter
- No limit was placed on the number of brain metastases

**Exclusion Criteria**

- Age < 18
- Absence of follow-up data at least 3 months following treatment
- Brain metastases >3 cm in diameter
- Patients treated with Gamma Knife (which was available at one institution but not the other two institutions), in order to minimize confounding of results based on technology availability

**Target Delineation and Dose comparison**

Target delineation, PTV margin expansion, dose prescription, and fractionation were at the discretion of the treating radiation oncologist. The biological effect of radiation treatment among the patients in our cohort was calculated using the biologically effective dose (BED\textsubscript{10}), which accounts for total dose and dose per fraction.\textsuperscript{12} BED\textsubscript{10} was calculated using the linear quadratic equation, with α/β set to 10, d equal to the dose per fraction in Gray units (Gy\textsubscript{10}), and n equal to the number of fractions delivered.

\[
BED_{\alpha/\beta} = d n \left(1 + \frac{d}{\alpha/\beta} \right)
\]

**Outcomes**

Patient outcome data were analyzed retrospectively in a de-identified manner. For intact brain metastases, tumor progression was assessed utilizing the Response Assessment in Neuro-Oncology Brain Metastases criteria defining progression as an increase in tumor diameter > 20% on interval MRIs.\textsuperscript{13} For resected brain metastases, progression was determined by the physician based upon clinical and radiographic findings. Local progression-free survival (LPFS) was defined for each metastasis as time from treatment completion to lesion progression of the targeted brain metastasis or death. Intracranial progression-free survival (ICPFS) was defined for each patient as time from treatment completion to any intracranial progression of disease or death. Overall survival (OS) was measured for each patient as time from treatment completion to death. Radionecrosis-free survival (RNFS) was measured for each metastasis as time from treatment completion to clinically apparent radionecrosis either by MRI or
pathology following surgical resection. For patients with both intact and resected brain metastases, metas-
tasis-level outcomes (LPFS and RNFS) were calculated
each individual metastasis; however, patient level
outcomes (ICPFS and OS) were calculated for each
patient based on the first metastasis that was treated.

Statistical Analysis

Patient characteristics were compared using the
independent sample t-test for numerical data and chi-
square analysis for categorical data. The Kaplan-Meier
method was used to compare LPFS, ICPFS, and OS
(stratified by intact versus resected metastases) as well
as RNFS (intact and resected metastases were com-
bined for analytic purposes due to a small number of
events). Data analysis was conducted using SPSS ver-
sion 22. Statistical significance was two-sided and set at
P < 0.05. Cox proportional hazards model was used to
adjust for differences in modality, sex, race, histology,
location, size, and number of metastases.

RESULTS

Patient Demographics and Tumor Variables

Baseline characteristics for patients receiving radio-
therapy to intact and resected brain metastases summa-
rized in Tables 1 and 2 respectively.

In total, 76 patients received radiotherapy to intact
brain metastases with SF-SRS (n=45) or HF-SRT
(n=31). Among these patients, 142 intact brain metas-
tases were treated with either SF-SRS (n=92) or HF-
SRT (n=50). The median dose and interquartile range
(IQR) for the SF-SRS group was 21 Gy (20-22 Gy)
with a median BED\textsubscript{10} and IQR of 65.1 Gy (60.0-70.4
Gy). The median number of metastases, IQR and
range for the SF-SRS group was 2, (1-3), and (1-7)
metastases. For the HF-SRT group, the most common
dose fractionation schemes were 24 Gy in 3 fractions
(n=16), 30 Gy in 5 fractions (n=13), 25 Gy in 5 frac-
tions (n=7), and 30 Gy in 3 fractions (n=7) with a
median BED\textsubscript{10} (IQR) of 43.2 Gy (37.5-48.0 Gy). The
median number of metastases, IQR, and range for the
HF-SRT group was 1, (1-5), and (1-8) metastases.

Table 1. Baseline characteristics for intact brain metastases treated with SF-SRS or HF-SRT

| Modality          | SF-SRS [n=92 (%)] | HF-SRT [n=50(%)] | p-value |
|-------------------|-------------------|------------------|---------|
| Sex               |                   |                  |         |
| Female            | 55 (59.7)         | 36 (72)          | 0.14722 |
| Male              | 37 (40.3)         | 14 (28)          |         |
| Race              |                   |                  |         |
| White             | 79 (85.8)         | 43 (86)          | 0.98297 |
| Non-White         | 13 (14.2)         | 7 (14)           |         |
| Histology         |                   |                  |         |
| Breast            | 15 (16.3)         | 16 (32)          | 0.00026 |
| Melanoma          | 8 (8.7)           | 4 (8)            |         |
| Lung              | 60 (65.2)         | 15 (30)          |         |
| Other             | 9 (9.8)           | 15 (30)          |         |
| Location          |                   |                  |         |
| Cerebral Cortex   | 66 (71.7)         | 27 (54)          |         |
| Cerebellum        | 18 (19.6)         | 12 (24)          | 0.04634 |
| Brainstem         | 8 (8.7)           | 11 (22)          |         |
| Number of Metastases |               |                  |         |
| Single            | 28 (30.4)         | 27 (54)          | 0.0059  |
| Multiple          | 64 (69.6)         | 23 (46)          |         |
| Size of Metastasis|                   |                  |         |
| ≤1.5 cm           | 85 (92.4)         | 31 (62)          | 0.00001 |
| >1.5 cm           | 7 (7.6)           | 19 (38)          |         |
brain metastases were treated with either SF-SRS (n=15) or HF-SRT (n=27). The median dose and IQR for the SF-SRS group was 18 Gy (15-18 Gy) with a median BED$_{10}$ and IQR of 50.4 Gy (37.5-50.4 Gy). The median number of metastases, IQR and range for the SF-SRS group was 1, (1-3), and (1-3) metastases. The most common dose fractionation schemes for the HF-SRT group were 25 Gy in 5 fractions (n=12), 30 Gy in 5 fractions (n=5), and 30 Gy in 3 fractions (n=3), with a median BED$_{10}$ (IQR) of 37.5 (37.5-50.4). The median number of metastases, IQR, and range for the HF-SRT group was 1, (1-2), and (1-3) metastases. There was no significant difference in pre-operative tumor diameter with a median diameter (IQR) of 1.9 cm (1.6-2.6 cm), mean of 1.9 cm and 73.3% of tumors >1.5 cm for the SF-SRS group and a median diameter (IQR) of 2.1 cm (1.6-2.6 cm), mean 2.0 cm and 77.8% of tumors >1.5 cm (p=0.7456). No significant differences existed between the two groups with race, tumor histology, number of metastases, or tumor location. Female patients (63% vs 37%; p=0.00756) were more likely to receive HF-SRT (Table 2).

| Modality | SF-SRS [n=15 (%)] | HF-SRT [n=27 (%)] | p-value |
|----------|------------------|-------------------|---------|
| Sex      |                  |                   |         |
| Female   | 3 (20)           | 17 (63)           | 0.00756 |
| Male     | 12 (80)          | 10 (37)           |         |
| Race     |                  |                   |         |
| White    | 12 (80)          | 26 (96.3)         | 0.08472 |
| Non-White| 3 (20)           | 1 (3.7)           |         |
| Histology|                  |                   |         |
| Breast   | 3 (20)           | 2 (7.4)           |         |
| Lung     | 7 (46.7)         | 5 (18.5)          | 0.09087 |
| Melanoma | 5 (30)           | 12 (44.4)         |         |
| Other    | 1 (3.3)          | 8 (29.6)          |         |
| Location |                  |                   |         |
| Cerebral Cortex | 13 (86.7) | 23 (85.2) | 0.89405 |
| Outside Cerebral Cortex | 2 (13.3) | 4 (14.8) |         |
| Number of Metastases |                    |                   |         |
| Single   | 8 (53.3)         | 14 (51.9)         | 0.92661 |
| Multiple | 7 (46.7)         | 13 (48.1)         |         |
| Size of Metastasis (diameter) |       |                   |         |
| ≤1.5 cm  | 4 (26.7)         | 6 (22.2)          | 0.74591 |
| >1.5 cm  | 11 (73.3)        | 21 (77.8)         |         |

Intact Brain Metastases

Local Progression-Free Survival

For intact brain metastases treated with SF-SRS or HF-SRT, with a median follow up time of 10 months, the estimated LPFS at 6 months, 12 months, and 18 months were 76.8%, 62.8%, and 46.8% for the SF-SRS group and 67.5%, 58.5%, and 45.3% in the HF-SRT group respectively. There was no statistically significant difference in LPFS between SF-SRS and HF-SRT (P=0.638) (Figure 1A). Correspondingly on multivariable analysis, HF-SRT was not associated with a change in LPFS (HR 0.932; 95% CI 0.497-1.750; p=0.828). Histology was the only independent predictor of LPFS on multivariable analysis with melanoma (HR 4.514; 95% CI 1.492-13.659; p=0.008), lung (HR 2.377; 95% CI 1.166-4.845; p=0.017), and other (non-breast, melanoma, or lung) (HR 7.558; 95% CI 2.974-19.205; p=0.000021), all associated with worse LPFS (Table S1). Lastly, since multiple HF-SRT fractionation regimens were used, we compared LPFS of patients treated with HF-SRT with BED$_{10}$ < 45 Gy and BED$_{10}$ ≥ 45 Gy and found no significant difference in LPFS (p=0.330) (Figure S1A).

Intracranial Progression-Free Survival

The Kaplan-Meier plot for ICPFS is shown in Figure 1B. The estimated ICPFS at 6 months, 12 months, and 18 months were 77.3%, 56.9%, and 44.4% for the SF-SRS group and 73.7%, 55.3%, and 49.8% in the HF-SRT group. There was no statistically significant difference in ICPFS between SF-SRS and HF-SRT (P=0.300). Correspondingly, on multivariable analysis HF-SRT was not associated with ICPFS (HR 0.817; 95% CI 0.311-2.147; p=0.681). There were no independent predictors of increased risk of intracranial progression on multivariable analyses (Table S1).

Overall Survival

The Kaplan-Meier plot for OS is shown in Figure 1C. The estimated OS at 6 months, 12 months, and 18 months...
The only predictor of worse survival on multivariable analysis was other histology (non-breast, melanoma, or lung) conferring a higher risk of death (HR 6.709; 95% CI 1.516-29.696; p=0.012) (Table S1).

**Radionecrosis-Free Survival**

There was a very low rate of radionecrosis in our entire study cohort. Specifically, the low overall number of events in the resected group precluded further statistical analysis. Therefore, in the next section combined RNFS data for both intact and resected are reported.

**Resected Brain Metastases**

**Local Progression-Free Survival**

For resected brain metastases, with a median follow up time of 11 months, the estimated ICPFS at 6 months, 12 months, and 18 months were 76.9%, 67.3%, and 50.5% for the SF-SRS group and 81.3%, 57.8%, and 44.5% for the HF-SRT group. There was no statistically significant difference between SF-SRS and HF-SRT as measured by LPFS (P=0.288) (Figure 2A). Correspondingly, HF-SRT was not associated with worse LPFS (HR 1.486; 95% CI 0.484-4.564; p=0.489). There were no significant predictors of LPFS identified on multivariable analyses (Table S2). Lastly, since multiple HF-SRT fractionation regimens were used, we compared LPFS of patients treated with HF-SRT with BED$_{10} < 45$ Gy and BED$_{10} ≥ 45$ Gy and found no significant difference in LPFS (p=0.462) (Figure S1B).

**Intracranial Progression-Free Survival**

The Kaplan-Meier plot for ICPFS is shown in Figure 2B. The estimated ICPFS at 6 months, 12 months, and 18 months were 77.8%, 64.8%, and 48.6% for the SF-SRS group and 77%, 57.4%, and 40.1% for the HF-SRT group. There was no statistically significant difference in ICPFS between the SF-SRS and HF-SRT groups (P=0.291). Likewise, on multivariable analysis HF-SRT was not associated with an ICPFS (HR 1.825; 0.523-6.367; p=0.345). There were no significant predictors of ICPFS identified on multivariable analyses (Table S2).

**Overall Survival**

The Kaplan-Meier plot for OS is shown in Figure 2C. The estimated OS at 6 months, 12 months, and 18 months were 77.8%, 64.8%, and 48.6% for the SF-SRS group and 77%, 57.4%, and 40.1% for the HF-SRT group. There was no statistically significant difference in OS between the SF-SRS and HF-SRT groups (P=0.096). On multivariable analysis there was also no difference in risk of death for HF-SRT (HR 0.557; 95% CI 0.199-1.557; p=0.264).
Radionecrosis-Free Survival

The Kaplan-Meier plot for RNFS for both intact and resected brain metastases combined is shown in Figure 3. These data were combined for analysis due to the low event rate and in particular the low overall number of events in the resected group which precluded further statistical analysis. The estimated RNFS at 6 months, 12 months, and 18 months were 97.8%, 92.0%, and 92.0% for the SF-SRS group and 98.7%, 92.0%, and 92.0% for the HF-SRT group. There was no statistically significant difference in RNFS between SF-SRS and HF-SRT (P=0.325). HF-SRT was not associated with RNFS (HR 1.233; 95% CI 0.270-5.634; p=0.787). There were no significant predictors of RNFS identified on multivariable analyses (Table S3).

DISCUSSION

We found no statistically significant differences between linear accelerator-based SF-SRS and HF-SRT in the control of brain metastases as measured by LPFS, ICPFS, OS, and RNFS for brain metastases up to 3 cm in size. Our observations are consistent with previous studies demonstrating similar clinical outcomes in both LPFS and OS between SF-SRS and HF-SRT both to intact and resected brain metastases.14-16 Our investigation is unique in being the first multi-institutional study exclusively focusing on linear accelerator-based radiosurgical treatments for smaller brain metastases stratified into intact versus resected cohorts.

In a previous case series, the OS at 1 year for intact brain metastases treated with SF-SRS and HF-SRT were not statistically different at 53.1% and 69.4%, respectively. A more recent large multi-institutional case series showed similar local control rates of 90% and 81% for SF-SRS and HF-SRT.16 Interestingly, a recent meta-analysis of 24 studies analyzing local control of brain metastases larger than 3 cm found a
local control rate of 77.6% for SF-SRS and 92.9% for HF-SRT at one year, suggesting an advantage for HF-SRT; however, single-arm studies were included in this analysis, potentially biasing the conclusions.\textsuperscript{17} For resected brain metastases, a recent meta-analysis suggested excellent local control rates of 84%, with a slight benefit to HF-SRT vs. SF-SRS 87% vs. 80%.\textsuperscript{18} Additionally, a large single-institutional analysis of post-operative SRS in over 500 patients showed 93% local control at 12 months and 63% intracranial control at 12 months.\textsuperscript{19} Similarly, a recent multi-institutional cohort study of 558 patients with resected brain metastases treated with HFRT found a high rate of local control of 84% at one year with low rates of radionecrosis of 8.6%.\textsuperscript{20} Our study adds to these findings, suggesting similar local control and overall survival rates for SF-SRS and HF-SRT for both intact and resected brain metastases up to 3 cm in size while offering the advantage of comparing these treatment arms directly at multiple institutions using linear accelerator-only treatment.

Prior studies have suggested lower rates of radionecrosis in HF-SRT; however, these studies focused on patients with larger brain metastases.\textsuperscript{6,11,15} In our study focusing on brain metastases up to 3 cm in size, we found similar low rates of radionecrosis between the SF-SRS and HF-SRT. Given the overall low rate of radionecrosis among brain metastasis up to 3 cm, this suggests that the reduction in risk of radionecrosis previously seen may be more notable for larger brain metastases, which have a higher baseline risk of this toxicity.

This study is limited by the differences in patient baseline characteristics discussed above, particularly the differences in tumor size between SF-SRS and HF-SRT in the intact brain metastasis cohort (though this was accounted for in the multivariable analysis). Additionally, non-standardized dose-fractionation schemes and treatment planning across institutions existed in our dataset. At the one institution with Gamma Knife, linear accelerator-based treatment was typically used for HF-SRT, since SF-SRS was usually performed with the Gamma Knife instead. We chose not to include Gamma Knife patients, however, since (1) it was only available at one of the three institutions; and (2) we aimed to minimize the risk of confounding given prior suggestions that Gamma Knife may be associated with differential outcomes compared to linear-accelerator-based radiosurgery.\textsuperscript{21} We also did not have detailed patient toxicity outcomes to compare SF-SRS and HF-SRT and were unable to analyze leptomeningeal disease as a specific patient outcome. Lastly, our data set is limited to radiotherapy to intact and resected metastases and did not include any patients with pre-operative radiotherapy, which has been suggested as a potential means to lower rates of radionecrosis and leptomeningeal disease compared to post-operative radiotherapy.\textsuperscript{22}

CONCLUSIONS

In this retrospective, multi-institutional analysis we found a similar efficacy profile of linear accelerator-based SF-SRS and HF-SRT for the management of both intact and resected brain metastases up to 3 cm. This suggests that SF-SRS may be preferred for tumors ≤3 cm due to a similar safety and efficacy profile and reduced number of fractions. Further prospective studies are warranted to confirm these results.

Supplementary information to this paper can be accessed from the electronic version.

ACKNOWLEDGEMENTS

Funding

There was no research support for this study.

Authors’ disclosure of personal conflicts of interest

Dr. Park reports honoraria from Rad Onc Questions, LLC (past not present) outside of the submitted work. Brett H. Diamond, Vikram Jairam, Shaharyar Zuberi, Jessie Y. Li, Timothy J. Marquis, and Charles E. Rutter declare that they have no conflicts of interest.

Author contributions

Conception and design: Brett H. Diamond, Vikram Jairam, Charles E. Rutter, Henry S. Park
Data collection: Brett H. Diamond, Vikram Jairam, Shaharyar Zuberi, Jessie Y. Li, Timothy J. Marquis
Data analysis and interpretation: Brett H. Diamond, Vikram Jairam, Henry S. Park
Manuscript writing: Brett H. Diamond, Henry S. Park
Final approval of manuscript: All authors

Ethical conduct of research

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 194 Helsinki declaration and its later amendments or comparable ethical standards. The study was IRB approved at Hartford Healthcare (E-HHC-2018-0020), UConn Health (18X-141-2), and Yale University (2000022356).
REFERENCES

1. Achrol AS, Rennert RC, Anders C, Soffietti R, Ahluwalia MS, Nayak L, Peters S, Avolland ND, Harsh GR, Steeg PS, Chang SD. Brain metastases. Nature Reviews Disease Primers. 2019; 5:5. DOI: 10.1038/s41572-018-0055-y

2. Kann BH, Park HS, Johnson SB, Chiang VL, Yu JB. Radiosurgery for brain metastases: Changing practice patterns and disparities in the United States. J Natl Compr Canc Netw. 2017; 15: 1494-1502. DOI: 10.6004/jnccn.2017.7003

3. Brown PD, Jaecle K, Ballman K V, Farace E, Cerhan JH, Keith Anderson S, Carrero JW, Barker FG, Deming R, Burri SH, Ménard C, Chung C, Steiber VW, Pollock BE, Galanis E, Buckner JC, Asher AL. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases a randomized clinical trial. JAMA - J Am Med Assoc. 2016; 31:401-409. DOI: 10.1001/jama.2016.9839

4. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatanan K, Kenjyo M, Oya N, Hiraoka S, Shioura H, Kunieda E, Inomata T, Hayakawa K, Katoh N, Kobashi G. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: A randomized controlled trial. J Am Med Assoc. 2006; 295:2483-2491. DOI: 10.1001/jama.295.21.2483

5. Brown PD, Ballman K V, Cerhan JH, Anderson SK, Carrero JW, Whiton AC, Greenspoon J, Parney IF, Laack NNI, Ashman JB, Bahary JP, Hadjipanayis CG, Urbanic JJ, Barker FG, Farace E, Khuntia D, Giannini C, Buckner JC, Galanis E, Roberge D. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol. 2017; 18:1049-1060. DOI: 10.1016/S1470-2045(17)30441-2

6. Eaton BR, La Riviere MJ, Kim S, Prabhu RS, Patel K, Kandula S, Oyesiku N, Olson J, Curran W, Shu HK, Crocker I. Hypofractionated radiosurgery has a better safety profile than single fraction radiosurgery for large resected brain metastases. J Neurooncol. 2015; 123:103-111. DOI: 10.1007/s11060-015-1767-4

7. Lischalk JW, Germann E, Collins SP, Nair MN, Nayak V V, Bhasin R, Voyeradis JM, Rudra S, Unger K, Collins BT. Five-fraction stereotactic radiosurgery (SRS) for single inoperable high-risk non-small cell lung cancer (NSCLC) brain metastases. Radiat Oncol. 2015; 10:216-223. DOI: 10.1186/s13034-015-0525-2

8. Kwon AK, Dibiase SJ, Wang B, Hughes SL, Milcarek B, Zhu Y. Hypofractionated stereotactic radiotherapy for the treatment of brain metastases. Cancer. 2009; 115: 890-898. DOI: 10.1002/cncr.24082

9. Ogura K, Mizowaki T, Ogura M, Sakanaka K, Arakawa Y, Miyamoto S, Hiraoka M. Outcomes of hypofractionated stereotactic radiotherapy for metastatic brain tumors with high risk factors. J Neurooncol. 2012; 109:425-432. DOI: 10.1007/s11060-012-0912-6

10. Traylor J, Habib A, Patel R, Muir M, Gadot R, Briere T, Yeboa DN, Li J, Rao G. Fractionated stereotactic radiotherapy for local control of resected brain metastases. J Neurooncol. 2019; 144: 343-350. DOI: 10.1007/s11060-019-03233-9

11. Minniti G, Scaringi C, Paolini S, Lanzetta G, Romano A, Cicone F, Osti M, Enrici RM, Esposito V. Single-Fraction Versus Multifraction (3 x 9 Gy) Stereotactic Radiosurgery for Large (≥2 cm) Brain Metastases: A Comparative Analysis of Local Control and Risk of Radiation-Induced Brain Necrosis. Int J Radiat Oncol. 2016;95:1142–1148. DOI: 10.1016/j.ijrobp.2016.03.013

12. Fowler JF. 21 Years of biologically effective dose. British Journal of Radiology. 2010;83:554-568. DOI: 10.1259/bjr/31372149

13. Lin NU, Lee EQ, Aoyama H, Barani J, Barbioriak DP, Baumert BG, Bendszus M, Brown PD, Camidge DR, Chang SM, Dancey J, de Vries EGE, Gaspar LE, Harris GJ, Hodi FS, Kalkanis SN, Linskey ME, Macdonald DR, Margolin K, Mehta MP, Schiff D, Soffietti R, Suh JH, van den Bent MJ, Vogelbaum MA, Wen PY. Response assessment criteria for brain metastases: Proposal from the RANO group. The Lancet Oncology. 2015;16:270-278. DOI: 10.1016/S1470-2045(15)70057-4

14. Kübler J, Wester-Ebbinghaus M, Wenz F, Stieler B, Bathein B, Mai SK, Wolff R, Hänggi D, Bianco G, Giordano F. Postoperative stereotactic radiosurgery and hypofractionated radiotherapy for brain metastases using Gamma Knife and CyberKnife: a dual-center analysis. J Neurosurg Sci. 2020. Ahead of print. 10.23736/S0390-5616.20.04830-4

15. Chon H, Yoon KJ, Lee D, Kwon DH, Cho YH. Single-fraction versus hypofractionated stereotactic radiosurgery for medium-sized brain metastases of 2.5 to 3 cm. J Neurooncol. 2019; 145:49-56. DOI: 10.1007/s11060-019-03265-1

16. Remick JS, Kowalski E, Khairmar R, Sun K, Morse E, Cheng HRR, Poirier Y, Lamichhane N, Becker SJ, Chen S, Patel AN, Kwok Y, Nichols E, Mohindra P, Woodworth GF, Regine WF, Mishra M V. A multi-center analysis of single-fraction versus hypofractionated stereotactic radiosurgery for the treatment of brain metastasis. Radiat Oncol. 2020; 15:128-139. DOI: 10.1186/s13034-020-01522-6

17. Lehrer EJ, Peterson JL, Zaorsky NG, Brown PD, Sahgal A, Chiang VL, Chao ST, Sheehan JP, Trifiletti DM. Single versus Multifraction Stereotactic Radiosurgery for Large Brain Metastases: An International Meta-analysis of 24 Trials. Int J Radiat Oncol Biol Phys. 2019; 103:S18-630. DOI: 10.1016/j.ijrobp.2018.10.038

18. Akanda ZZ, Hong W, Nahavandi S, Haghhighi N, Phillips C, Kok DL. Post-operative stereotactic radiosurgery following excision of brain metastases: A systematic review and meta-analysis. Radiotherapy and Oncology. 2020; 142:27-35. DOI: 10.1016/j.ijrobp.2019.08.024

19. Shi S, Sandhu N, Wang EH, Liu E, Jaoude JA, Jin M, Schofield K, Zhang C, Gibbs IC, Hancock SL, Chang SD, Li G, Hayden M, Soltsy SG, Pollom E. Stereotactic Radiosurgery for Resected Brain Metastases: Single-Institutional Experience of over 500 Cavities. Int J Radiat Oncol. 2019; 106:764-771. DOI: 10.1016/j.ijrobp.2019.11.022
20. Eitz KA, Lo S, Soliman H, Sahgal A, Theriault A, Pinkham MB, Foote MC, Song AJ, Shi W, Redmond KJ, Gui C, Kumar A, Machtay M, Meyer B, Combs SE. Multi-institutional Analysis of Prognostic Factors and Outcomes After Hypofractionated Stereotactic Radiotherapy to the Resection Cavity in Patients with Brain Metastases. JAMA Oncology. 2020; Online in press. DOI: 10.1001/jamaoncol.2020.4630

21. Shaw E, Scott C, Souhami L, Dinapoli R, Kline R, Loeffler J, Faman N. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: Final report of RTOG protocol 90-05. Int J Radiat Oncol Biol Phys. 2000; 47:291-298. DOI: 10.1016/s0360-3016(99)00507-6

22. Kandula S, Zhong J, Press RH, Olson JJ, Oyesiku NM, Wait SD, Curran WJ, Shu HKG, Prabhu RS. Comparing preoperative with postoperative stereotactic radiosurgery for resectable brain metastases: A multi-institutional analysis. Neurosurgery. 2016; 79:279-285. DOI: 10.1227/NEU.0000000000001096