

ONLINE ONLY

Supplemental material

Two-stage radiosurgery for large brain metastases: a systematic review and meta-analysis of clinical outcomes

Terry et al.

<https://thejns.org/doi/abs/10.3171/2023.5.FOCUS23232>

DISCLAIMER The *Journal of Neurosurgery* acknowledges that the following section is published verbatim as submitted by the authors and did not go through either the *Journal's* peer-review or editing process.

Supplementary Table 1. Search strategy.

Database	Search strategy	Results
Pubmed/Medline	<p>#1 (“brain neoplasms”[Mesh] OR “brain neoplasm*”[TIAB] OR “brain tumor*”[TIAB] OR “brain cancer*”[TIAB] OR “Intracranial neoplasm*” [TIAB] OR “Cancer of Brain”[TIAB] OR “Cancer of the Brain”[TIAB] OR (“Brain”[Mesh] OR brain[TIAB] OR Encephalon[TIAB]) AND (“Neoplasm Metastasis”[Mesh] OR metasta*[TIAB])) AND Large[TIAB]</p> <p>#2 (Radiosurgery [MH] OR radiosurg*[TIAB] OR “Stereotactic radi*”[TIAB] OR “Linear accelerator radi*”[TIAB] OR “LINAC radi*”[TIAB] OR “Stereotactic body radi*”[TIAB] OR “CyberKnife radi*”[TIAB])</p> <p>#3 (“proton therapy”[MH] OR “proton therap*”[TIAB] OR “proton beam therapy”[TIAB] OR “proton beam radiation therapy”[TIAB])</p> <p>#4 #1 AND (#2 OR #3)</p>	832
Scopus	<p>#1 TITLE-ABS-KEY((“brain neoplasm*” OR “brain tumor*” OR “brain cancer*” OR “Intracranial neoplasm*” OR “Cancer of Brain” OR “Cancer of the Brain” OR ((brain OR Encephalon) AND (metasta*))) AND Large)</p> <p>#2 TITLE-ABS-KEY(radiosurg* OR “Stereotactic radi*” OR “Linear accelerator radi*” OR “LINAC radi*” OR “Stereotactic body radi*” OR “CyberKnife radi*”)</p> <p>#3 TITLE-ABS-KEY(“proton therap*” OR “proton beam therapy” OR “proton beam radiation therapy”)</p> <p>#4 #1 AND (#2 OR #3)</p>	1019
Web Of Science/Scielo	<p>#1 TI=((“brain neoplasm*” OR “brain tumor*” OR “brain cancer*” OR “Intracranial neoplasm*” OR “Cancer of Brain” OR “Cancer of the Brain” OR ((brain OR Encephalon) AND (metasta*))) AND Large) OR TS=((“brain neoplasm*” OR “brain tumor*” OR “brain cancer*” OR “Intracranial neoplasm*” OR “Cancer of Brain” OR “Cancer of the Brain” OR ((brain OR Encephalon) AND (metasta*))) AND Large) OR KP=((“brain neoplasm*” OR “brain tumor*” OR “brain cancer*” OR “Intracranial neoplasm*” OR “Cancer of Brain” OR “Cancer of the Brain”</p>	1,157

OR ((brain OR Encephalon) AND (metasta*)) AND Large) OR
AK=((“brain neoplasm*” OR “brain tumor*” OR “brain
cancer*” OR “Intracranial neoplasm*” OR “Cancer of Brain”
OR “Cancer of the Brain” OR ((brain OR Encephalon) AND
(metasta*)) AND Large) OR AB=((“brain neoplasm*” OR
“brain tumor*” OR “brain cancer*” OR “Intracranial
neoplasm*” OR “Cancer of Brain” OR “Cancer of the Brain”
OR ((brain OR Encephalon) AND (metasta*)) AND Large)

#2 TI=(radiosurg* OR “Stereotactic radi*” OR “Linear
accelerator radi*” OR “LINAC radi*” OR “Stereotactic body
radi*” OR “CyberKnife radi*”) OR TS=(radiosurg* OR
“Stereotactic radi*” OR “Linear accelerator radi*” OR “LINAC
radi*” OR “Stereotactic body radi*” OR “CyberKnife radi*”)
OR KP=(radiosurg* OR “Stereotactic radi*” OR “Linear
accelerator radi*” OR “LINAC radi*” OR “Stereotactic body
radi*” OR “CyberKnife radi*”) OR AK=(radiosurg* OR
“Stereotactic radi*” OR “Linear accelerator radi*” OR “LINAC
radi*” OR “Stereotactic body radi*” OR “CyberKnife radi*”)
OR AB=(radiosurg* OR “Stereotactic radi*” OR “Linear
accelerator radi*” OR “LINAC radi*” OR “Stereotactic body
radi*” OR “CyberKnife radi*”)

#3 TI=(“proton therap*” OR “proton beam therapy” OR
“proton beam radiation therapy”) OR TS=(“proton therap*” OR
“proton beam therapy” OR “proton beam radiation therapy”) OR
KP=(“proton therap*” OR “proton beam therapy” OR “proton
beam radiation therapy”) OR AK=(“proton therap*” OR “proton
beam therapy” OR “proton beam radiation therapy”) OR
AB=(“proton therap*” OR “proton beam therapy” OR “proton
beam radiation therapy”)

#4 1 AND (#2 OR #3)

Embase #1 ('brain metastasis'/exp OR 'brain metastasis':ti,ab,kw OR 851
'brain metastatic tumor':ti,ab,kw OR 'brain metastatic
tumour':ti,ab,kw OR 'brain tumor metastasis':ti,ab,kw OR 'brain
tumour metastasis':ti,ab,kw OR 'cerebral metastasis':ti,ab,kw
OR 'metastasis, brain':ti,ab,kw) AND large:ti,ab

#2 ('radiosurgery'/exp OR 'radio-surgery':ti,ab,kw OR
'radiosurgery':ti,ab,kw)

#3 'proton therapy'/exp OR 'proton beam radiotherapy':ti,ab,kw
OR 'proton beam therapy':ti,ab,kw OR 'proton radiation

	therapy':ti,ab,kw OR 'proton radiotherapy':ti,ab,kw OR 'proton therapy':ti,ab,kw	
	#4 #1 AND (#2 OR #3)	
Cochrane (OvidSP)	#1 ([mh "brain neoplasms/secondary"] OR ("Brain" NEXT tumor*):ti,ab OR ("Benign brain" NEXT neoplasm*):ti,ab OR ("Intracranial" NEXT neoplasm*):ti,ab OR "Recurrent brain tumor":ti,ab OR ("Brain" NEXT metastase*):ti,ab OR ("Brain malignant" NEXT neoplasm*):ti,ab OR ("Malignant brain" NEXT neoplasm*):ti,ab) AND (large*:ti,ab)	149
	#2 ([mh "Neoplasm Metastasis"] OR Metastase*:ti,ab OR ("Neoplasm" NEXT metastas*):ti,ab OR metastatic*:ti,ab)	
	#3 (ophthalmic or extracranial).ti,ot,sh,kw,ab.	
	#4 ([mh "proton therapy"] OR "proton beam therapy":ti,ab OR "proton beam radiation therapy":ti,ab)	
	#5 ((#1 AND #2) AND (#3 OR #4))	
Google scholar	#1 ((brain AND metasta*) AND Large)	First 100
	#2 (radiosurg* OR "Stereotactic radi*" OR "proton therapy")	
	#3 #1 AND #2	

***Results until December 14, 2022**

Supplementary Table 2. List of excluded studies

Author-year	Title	Exclusion reasons
Cho-2022 ¹	How to dose-stage large or high-risk brain metastases: an alternative two-fraction radiosurgical treatment approach	Wrong intervention
Medvedeva-2022 ²	Two-stage Gamma Knife radiosurgery for brain metastases	Wrong population
Yomo-2022 ³	Staged radiosurgery alone versus postoperative cavity radiosurgery for patients with midsize-to-large brain metastases: a propensity score matching analysis	Wrong population
Rozati-2021 ⁴	Three-staged stereotactic radiosurgery for brain metastases: A single institution experience	Wrong publication type
Cui-2020 ⁵	A Novel Methodology To Evaluate Radiation Dose To Brain For Dose-Staged Stereotactic Radiosurgery	Wrong publication type
Kim-2020 ⁶	Two-staged gamma knife radiosurgery for treatment of numerous (>10) brain metastases	Wrong population
Damron-2020 ⁷	Volume kinectis following two-session gamma knife radiosurgery for large brain metastases (BM)	Wrong publication type
Hori-2020 ⁸	Efficacy and long-term outcomes in the management of large brain metastasis (≥ 4 cm ³) using 2-staged stereotactic radiosurgery (2-SSRS): An international study	Wrong publication type
Park-2019 ⁹	Single-Session versus Multisession Gamma Knife Radiosurgery for Large Brain Metastases from Non-Small Cell Lung Cancer: A Retrospective Analysis	Wrong intervention
Yomo-2019 ¹⁰	Single- versus 2-session Gamma Knife surgery for symptomatic midsize brain metastases	Wrong population
Frischer-2016 ¹¹	Evaluation of Dose-Staged Gamma Knife Radiosurgical Treatment Method for High-Risk Brain Metastases	Wrong population
Lee-2015 ¹²	Comparative Analysis of Efficacy and Safety of Multisession Radiosurgery to Single Dose Radiosurgery for Metastatic Brain Tumors	Wrong population
Akabane-2013 ¹³	Staged Gamma Knife Radiosurgery for Relatively Large Metastatic Brain Tumors	Wrong publication type
Minniti-2013 ¹⁴	Multidose Stereotactic Radiosurgery (9 Gy x 3) of the Postoperative Resection Cavity for Treatment of Large Brain Metastases	Wrong population
Inoue-2012 ¹⁵	Optimal multisession radiosurgery for large brain metastases in critical areas	Wrong publication type
Terahara-2000 ¹⁶	Analysis of dose distribution in gamma knife radiosurgery for multiple targets	Wrong population

Supplementary Table 3. Volumetric (cm³) and survival data aggregated by intervention.

Study	No LBM (n)	Mean initial volume	Mean post-GKRS1 volume	Mean volume at LFU	Relative volume reduction from Baseline-LFU	Median overall survival, med(range) months	Progression-free survival, med(range) months
Two-staged GammaKnife radiosurgery (GKRS)							
Cui,2022 ¹⁷	24	10.7 ± 4.45	5.61 ± 4.1	NR	48.58 ± 22.11	NR	NR
Damron, 2022 ¹⁸	26	9.88 ± 6.82	5.92 ± 6.39	3.19 ± 4.35	NR	7.3	9.1
Ginalis, 2020 ¹⁹	23	10.38 ± 4.38	5.68 ± 4.41	NR	85.8**	NR	5.07 (3.53-5.23)
Ito, 2020 ²⁰	NR	NR	NR	NR	NR	6.6 (5.3-9.3) [‡]	NR
Lovo, 2019 ²¹	22	12.3 (7-78.4)*	NR	4.1 ± 1.3-70*	66	24 (3-32) ^{‡‡}	8 (5-20) ^{‡‡}
Serizawa, 2019 ²²	336	17.1 ± 5.9	NR	11.7 ± 6.7	31.7 ± 31.4	11.7	NR
Angelov, 2018 ²³	63	11.46 ± 6.2	8.27 ± 6.16	5.15 ± 4.93	49 ± 35.25	10.8 (4.9-26.0) [‡]	5.2 (1.3-7.4)
Dohm,2018 ²⁴	39	15.6 ± 14	10.37 ± 9.91	NR	NR	7.7	NR
Dohm,2018 ²⁵	45	17.28 ± 12.35	10.29 ± 9.42	NR	36	13.2	NR
Yomo,2014 ²⁶	61	18.98 ± 9.94	11 ± 8.69	NR	NR	11.8 (5.5-15.6)	NR
Yomo,2012 ²⁷	28	21.23 ± 10.76	9.7**	NR	NR	11.9 (4.67-15.63)	NR
Three-staged GammaKnife radiosurgery (GKRS)							
Serizawa, 2019 ²²	149	19.4 ± 6.7	NR	12 ± 7.3	37.4 ± 33.9	15.9	NR
Yamamoto, 2018 ²⁸	NR	NR	NR	NR	NR	8.3 (5.3-10.6)	NR
Higuchi,2009 ²⁹	46	17.6 ± 6.3	14.3 ± 6.5	10.6 ± 6.1	NR	8.8	NR

*Mean (range)

**Median

[‡]95% Confidence Interval (CI)

^{‡‡}Mean

LBM: Large Brain metastases, LFU: Last follow-up, GKS: GammaKnife session, NR: Not reported

Volume at LFU: Post-GKRS2 or Post-GKRS3 volume accordingly

Supplementary Figure 1. Risk Of Bias In Non-randomized Studies of Interventions-ROBINS-I




Study	Risk of bias domains							Overall
	D1	D2	D3	D4	D5	D6	D7	
Damron et al.; 2022 ¹⁸	⊗	⊕	⊕	⊕	⊕	⊖	⊕	⊗
Ginalis et al.; 2020 ¹⁹	⊗	⊕	⊕	⊕	⊕	⊖	⊕	⊗
Ito et al.; 2020 ²⁰	⊗	⊕	⊕	⊕	⊕	⊖	⊖	⊗
Serizawa et al.; 2019 ²²	⊗	⊕	⊖	⊕	⊕	⊖	⊖	⊗
Angelov et al.; 2018 ²³	⊖	⊕	⊕	⊕	⊕	⊖	⊕	⊖
Dohm et al.; 2018 ²⁴	⊕	⊕	⊕	⊕	⊕	⊖	⊖	⊖
Dohm et al.; 2018 ²⁵	⊕	⊕	⊕	⊕	⊕	⊖	⊖	⊖
Yamamoto et al.; 2018 ²⁸	⊖	⊕	⊕	⊕	⊕	⊖	⊖	⊖
Hasegawa et al.; 2017 ³⁰	⊗	⊕	⊕	⊕	⊖	⊖	⊕	⊗
Yomo et al.; 2014 ²⁶	⊕	⊕	⊕	⊕	⊕	⊖	⊕	⊖
Yomo et al.; 2012 ²⁷	⊗	⊕	⊕	⊕	⊕	⊖	⊕	⊗
Higuchi et al.; 2009 ²⁹	⊗	⊕	⊕	⊕	⊕	⊖	⊕	⊗

Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

Judgement
⊗ Serious
⊖ Moderate
⊕ Low

Supplementary Figure 2. Risk Of Bias The *Joanna Briggs Institute (JBI)* tool for assessing case series

		JBI risk of bias assessment tool									
Study design		Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10
Cui et al.; 2022 ¹⁷	Case series	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Not applicable
Lovo et al.; 2019 ²¹	Case series	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Not applicable

 Yes
 No
 Not applicable

Items

1. Where there clear criteria for inclusion in the case series ?
2. Was the condition measured in a standard reliable way for all participants included in the case series?
3. Were valid methods used for identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow-up results of cases clearly reported?
9. Was there clear reporting of the presenting sites/clinics demographic information?
10. Was statistical analysis appropriate?

Item questions reproduced from Munn Z, Barker TH, Moola S, Tufanaru C, Stern C, McArthur A, Stephenson M, Aromataris E. Methodological quality of case series studies: an introduction to the JBI critical appraisal tool. *JBI Evidence Synthesis*. 2020;18(10):2127-2133. © Joanna Briggs Institute, published with permission.

Supplementary References

1. Cho A, Medvedeva K, Kranawetter B, et al. How to dose-stage large or high-risk brain metastases: an alternative two-fraction radiosurgical treatment approach. *J Neurosurg.* 2022;137(6):1666-1675. doi:10.3171/2022.2.JNS212440
2. Medvedeva KE, Baulin AA, High-precision Radiology Center Gamma-Clinic (Gamma-Medtechnologii LLC), et al. Two-stage Gamma Knife radiosurgery for brain metastases. *Radiat Risk Bull Natl Radiat Epidemiol Regist.* 2022;31(1):136-149. doi:10.21870/0131-3878-2022-31-1-136-149
3. Yomo S, Yako T, Kitazawa K, Oguchi K. Staged radiosurgery alone versus postoperative cavity radiosurgery for patients with midsize-to-large brain metastases: a propensity score matching analysis. *J Neurosurg.* Published online December 17, 2021:1-8. doi:10.3171/2021.9.JNS211797
4. Rozati H, Paddick I, Sabin I. Three-staged stereotactic radiosurgery for brain metastases: a single institution experience. *Neuro-Oncol.* 2021;23(Supplement_4):iv20-iv21. doi:10.1093/neuonc/noab195.052
5. Cui T, Nie K, Weiner JP, Chundury A, Yue NJ, Danish S. A Novel Methodology To Evaluate Radiation Dose To Brain For Dose-Staged Stereotactic Radiosurgery. *Int J Radiat Oncol Biol Phys.* 2020;108(3):e730. doi:10.1016/j.ijrobp.2020.07.123
6. Kim M, Cho KR, Choi JW, et al. Two-staged gamma knife radiosurgery for treatment of numerous (>10) brain metastases. *Clin Neurol Neurosurg.* 2020;195:105847. doi:10.1016/j.clineuro.2020.105847
7. Damron E, Esquenazi Y, Tandon N, et al. RADT-06. VOLUME KINETICS FOLLOWING TWO-SESSION GAMMA KNIFE RADIOSURGERY FOR LARGE BRAIN METASTASES (BM). *Neuro-Oncol.* 2020;22(Suppl 2):ii182. doi:10.1093/neuonc/noaa215.760
8. Hori Y, Yomo S, Wei W, et al. INNV-03. EFFICACY AND LONG-TERM OUTCOMES IN THE MANAGEMENT OF LARGE BRAIN METASTASIS (≥ 4 CM³) USING 2-STAGED STEREOTACTIC RADIOSURGERY (2-SSRS): AN INTERNATIONAL STUDY. *Neuro-Oncol.* 2020;22(Suppl 2):ii117. doi:10.1093/neuonc/noaa215.487
9. Park K, Kim JW, Chung HT, Paek SH, Kim DG. Single-Session versus Multisession Gamma Knife Radiosurgery for Large Brain Metastases from Non-Small Cell Lung Cancer: A Retrospective Analysis. *Stereotact Funct Neurosurg.* 2019;97(2):94-100. doi:10.1159/000496154
10. Yomo S, Oda K, Oguchi K. Single- versus 2-session Gamma Knife surgery for symptomatic midsize brain metastases: a propensity score-matched analysis. *J Neurosurg.* Published online October 18, 2019:1-9. doi:10.3171/2019.7.JNS191193
11. Frischer JM, Fraller A, Mallouhi A, et al. Evaluation of Dose-Staged Gamma Knife Radiosurgical Treatment Method for High-Risk Brain Metastases. *World Neurosurg.* 2016;94:352-359. doi:10.1016/j.wneu.2016.07.038

12. Lee GS, Cho SJ, Kim JH, et al. Comparative Analysis of Efficacy and Safety of Multisession Radiosurgery to Single Dose Radiosurgery for Metastatic Brain Tumors. *Brain Tumor Res Treat.* 2015;3(2):95-102. doi:10.14791/btrt.2015.3.2.95
13. Akabane A, Kanazawa I, Ochiai C. Staged Gamma Knife Radiosurgery for Relatively Large Metastatic Brain Tumors. 2013;91(0):57-57.
14. Minniti G, Esposito V, Clarke E, et al. Multidose stereotactic radiosurgery (9 Gy × 3) of the postoperative resection cavity for treatment of large brain metastases. *Int J Radiat Oncol Biol Phys.* 2013;86(4):623-629. doi:10.1016/j.ijrobp.2013.03.037
15. Inoue H, Seto K, Nozake A, et al. Optimal multisession radiosurgery for large brain metastases in critical areas. 2012;90(0):106. doi:https://doi-org.ezproxy.uthsc.edu/10.1159/000342226
16. Terahara A, Machida T, Kubo T, Aoki Y, Ohtomo K. Analysis of dose distribution in gamma knife radiosurgery for multiple targets. *Int J Radiat Oncol Biol Phys.* 2000;47(5):1431-1434. doi:10.1016/s0360-3016(00)00483-1
17. Cui T, Weiner J, Danish S, et al. Evaluation of Biological Effective Dose in Gamma Knife Staged Stereotactic Radiosurgery for Large Brain Metastases. *Front Oncol.* 2022;12. <https://www.frontiersin.org/articles/10.3389/fonc.2022.892139>
18. Damron EP, Dono A, Chafi H, et al. Metastatic Neoplasm Volume Kinetics Following 2-Stage Stereotactic Radiosurgery. *World Neurosurg.* 2022;161:e210-e219. doi:10.1016/j.wneu.2022.01.109
19. Ginalis EE, Cui T, Weiner J, Nie K, Danish S. Two-staged stereotactic radiosurgery for the treatment of large brain metastases: Single institution experience and review of literature. *J Radiosurgery SBRT.* 2020;7(2):105-114.
20. Ito D, Aoyagi K, Nagano O, Serizawa T, Iwadate Y, Higuchi Y. Comparison of two-stage Gamma Knife radiosurgery outcomes for large brain metastases among primary cancers. *J Neurooncol.* 2020;147(1):237-246. doi:10.1007/s11060-020-03421-y
21. Lovo EE, Torres B, Campos F, et al. Evaluation of Dose-Staged Gamma Knife Radiosurgical Treatment Method for High-Risk Brain Metastases - ClinicalKey. *Cureus J Med Sci.* 2019;11(8):e5472. doi:10.7759/cureus.5472
22. Serizawa T, Higuchi Y, Yamamoto M, et al. Comparison of treatment results between 3- and 2-stage Gamma Knife radiosurgery for large brain metastases: a retrospective multi-institutional study. *J Neurosurg.* 2018;131(1):227-237. doi:10.3171/2018.4.JNS172596
23. Angelov L, Mohammadi AM, Bennett EE, et al. Impact of 2-staged stereotactic radiosurgery for treatment of brain metastases ≥ 2 cm. *J Neurosurg.* 2018;129(2):366-382. doi:10.3171/2017.3.JNS162532

24. Dohm A, McTyre ER, Okoukoni C, et al. Staged Stereotactic Radiosurgery for Large Brain Metastases: Local Control and Clinical Outcomes of a One-Two Punch Technique. *Neurosurgery*. 2018;83(1):114-121. doi:10.1093/neuros/nyx355
25. Dohm AE, Hughes R, Wheless W, et al. Surgical resection and postoperative radiosurgery versus staged radiosurgery for large brain metastases. *J Neurooncol*. 2018;140(3):749-756. doi:10.1007/s11060-018-03008-8
26. Yomo S, Hayashi M. A minimally invasive treatment option for large metastatic brain tumors: long-term results of two-session Gamma Knife stereotactic radiosurgery. *Radiat Oncol Lond Engl*. 2014;9:132. doi:10.1186/1748-717X-9-132
27. Yomo S, Hayashi M, Nicholson C. A prospective pilot study of two-session Gamma Knife surgery for large metastatic brain tumors. *J Neurooncol*. 2012;109(1):159-165. doi:10.1007/s11060-012-0882-8
28. Yamamoto M, Higuchi Y, Serizawa T, et al. Three-stage Gamma Knife treatment for metastatic brain tumors larger than 10 cm³: a 2-institute study including re-analyses of earlier results using competing risk analysis. *J Neurosurg*. 2018;129(Suppl1):77-85. doi:10.3171/2018.7.GKS181392
29. Higuchi Y, Serizawa T, Nagano O, et al. Three-staged stereotactic radiotherapy without whole brain irradiation for large metastatic brain tumors. *Int J Radiat Oncol Biol Phys*. 2009;74(5):1543-1548. doi:10.1016/j.ijrobp.2008.10.035
30. Hasegawa T, Kato T, Yamamoto T, et al. Multisession gamma knife surgery for large brain metastases. *J Neurooncol*. 2017;131(3):517-524. doi:10.1007/s11060-016-2317-4