Supplemental Online Content

Chen WC, Baal US, Baal JD, et al. Efficacy and safety of stereotactic radiosurgery for brainstem metastases: a systematic review and meta-analysis. *JAMA Oncol*. Published online May 13, 2021. doi:10.1001/jamaoncol.2021.1262

This supplemental material has been provided by the authors to give readers additional information about their work.

eMETHODS

References from identified BSM studies and review articles were analyzed to identify additional candidate studies. Case reports were excluded, as were studies in which characteristics and outcomes of BSM could not be disaggregated from other tumor types, studies focused on technical or other non-clinical aspects of SRS, and studies containing duplicate reports of overlapping datasets. After identifying candidate studies, data extraction for BSM studies was performed independently by 2 of 3 authors (WCC, JDB, UB), and discrepancies resolved by consensus and through discussions with the senior authors (SEB, DRR). SRS doses were converted to biological effective dose (BED10) with alpha/beta ratio of 10 using the linear quadratic formula[1]. Maximum SRS dose, if not reported, was estimated by dividing the prescribed SRS dose by the prescription isodose percentage. If numeric 1- or 2-year LC/OS were not reported in the text, values was estimated by digitizing Kaplan-Meier curves and overlaying grids to resolve outcomes to 1% accuracy. The outcome of interest was estimated and rounded to the nearest 1%.

A search for "(srs OR stereotactic OR radiosurgery OR knife) AND (brain/exp) AND (metastasis/exp OR metastasis OR metastases/exp OR metastases OR metastatic)", and filter for "clinical trial" was undertaken to identify prospective trials of non-brainstem metastases published between 2000 and December 2019, in order to match the timespan of identified BSM studies. Studies of hypofractionated radiotherapy, investigation of systemic therapy treatment of BM, secondary analyses of previous trials, limited analyses of niche radioresistant histologies, and trials failing to accrue resulting in early cessation (<25% of target accrual and <50 patients), were excluded (Supplemental Figure 1B).

A similar approach was used to identify trials of targeted and immunotherapy for BM from non-small cell lung, melanoma, breast, and renal cell carcinoma. A list of Food and Drug Administration (FDA) approved targeted therapies for these cancers was obtained from National Cancer Institute's Targeted Cancer Therapy Fact Sheet[2]. A search for these drug names or the term "immunotherapy" and the term "brain metastasis", filtered for clinical trials, was performed on December 20, 2020. For non-small cell lung, agents for the most common pathogenic gene alterations (*EGFR, ALK, ROS*) were conducted for included

crizotinib, alectinib, ceritinib, next-generation *EGFR* inhibitor osimertinib, necitumumab, lorlatinib, dacomitinib. Targeted agents for rare *RET* rearrangement, *MET* exon 14 skip mutation, and other rare alterations were excluded for the purposes of this analysis. For breast cancer, agents included alpelisib (*PI3K*), *HER2/Neu* targeted agents including trastuzumab and pertuzumab, lapatinib, neratinib, tucatinib, afatinib, as well as *PARPi* and *CDK4/6i* including olaparib, palbociclib, ribociclib, and abemaciclib. *BRAF* targeted agents, including dabrafenib, trametinib, were included for melanoma. Intracranial overall response rates were extracted, along with the response criteria, and detailed trial characteristics can be found in Supplemental Table 2. Non-negative studies (IC-ORR >= 10%) were included in quantitative meta-analysis.

In addition, a search of "srs" and "brain metastases" in *clinicaltrials.gov* was performed on December 20, 2020, and results were filtered for "recruiting, or active, not yet recruiting, or active, not recruiting", and Phase I-III studies. Trials studying SRS before/after surgical resection were excluded. Study quality was assessed using Methodological Index for Non-Randomized Studies (MINORS) criteria[3], and Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines were followed[4].

Both fixed and random-effects models are displayed, but results of more conservative random-effects models are reported in the text. We chose to perform and display both fixed-effect and random-effect models in our figures, but reported random-effect models in the text of our manuscript for 3 reasons. First, the level of I^2 heterogeneity for the various endpoints studied was never 0%, indicating the presence of at least some heterogeneity, a finding which is to be expected in an examination of studies across various institutions and settings. Necessarily, when $I^2>0$, the confidence interval around a random effects model is wider than that of a fixed effect model, and in this way a random effects model is the more conservative of the two. Second, the assumptions underlying a random effects model were felt to be more reasonable in this clinical setting, i.e that the observed differences among studies were due to both random chance and underlying variation in the intervention effects across settings and institutions. Third, the small sample effect, wherein smaller studies are weighted relatively more heavily in a random-effects versus a fixed effect analysis, was

not felt to be a major concern given that the majority of studies were of a similar and small size. In support of this hypotheses, we found fixed and random effects estimates closely mirrored one another for all endpoints studied.

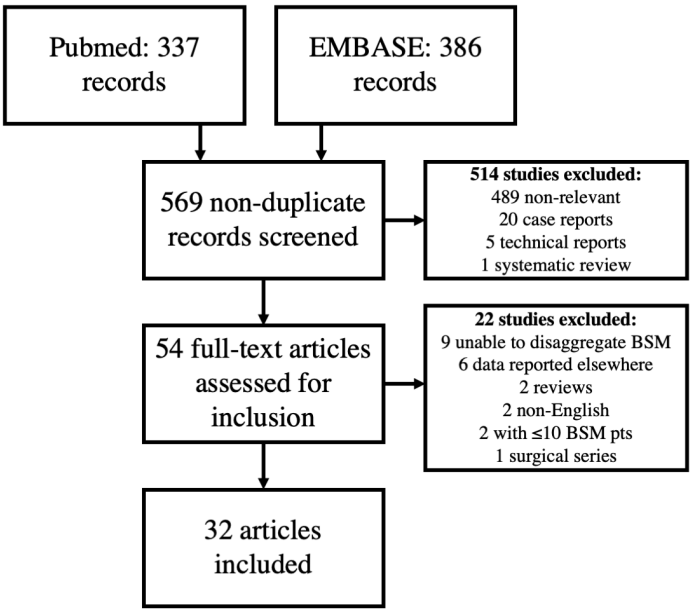
Publication bias was assessed with funnel plots of sample size rather than standard error versus treatment effect when proportions tended to the extreme (>80% and <20%), as the standard error can be biased in meta-analysis of proportions when proportions are close to an extreme[5]. Publication bias was tested via Egger's regression test using the *regtest* function within the *metafor* package in R.

Most studies ascribed neurologic death based upon criteria previously established by Patchell et al[6], scoring events when patients died of progressive neurologic dysfunction from brain metastases and/or leptomeningeal disease, or when patients had evidence of severe neurologic dysfunction at time of death (Supplement 1). Symptom prevalence and response/improvement was typically reported in a narrative fashion, rather than with pre-defined criteria, which is a possible limitation of this particular analysis. Clinically significant toxicity was uniformly commented upon in all studies. However, a limitation of retrospective studies is that minor toxicities may not have been well documented and thus may be under-reported. The overall risk of bias in included studies was assessed to be low, and 31 of the 32 studies received a score of 10 or greater out of 12 total possible points (Supplement 1). Studies most commonly lost points due to absence of blinded review of subjective endpoints. Both imaging and clinical follow up were generally adequate given the short median survival of this patient population.

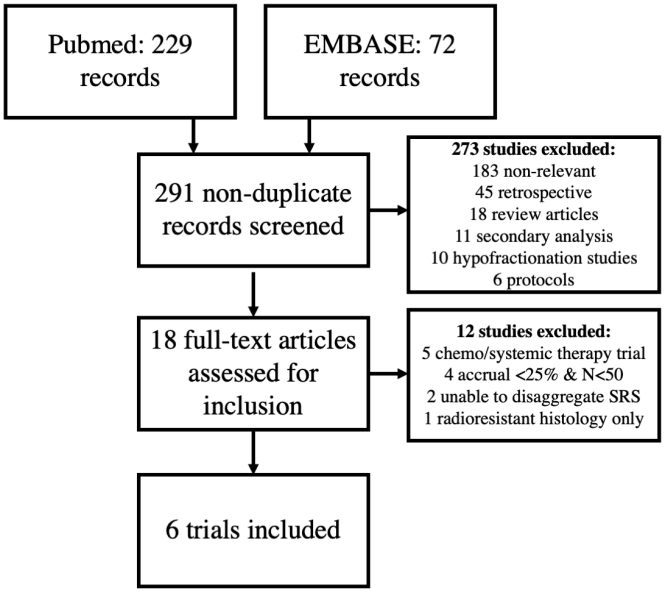
SUPPLEMENTAL FIGURES AND TABLES
eFigure 1. PRISMA flowcharts

PRISMA flowcharts are shown for BSM SRS studies (A) and prospective BM SRS trials (B).

A)

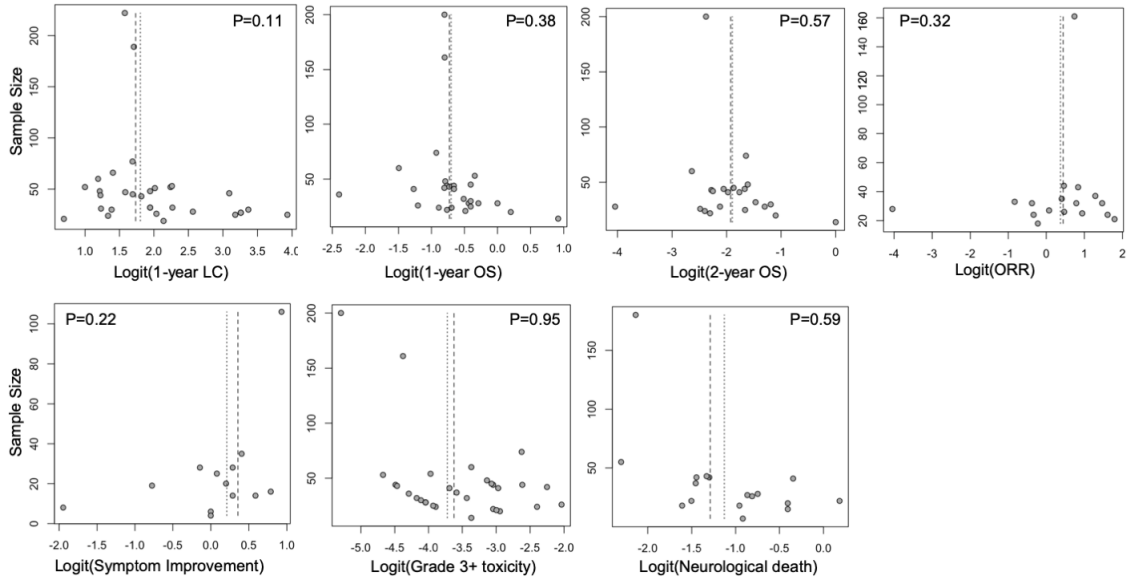


B)



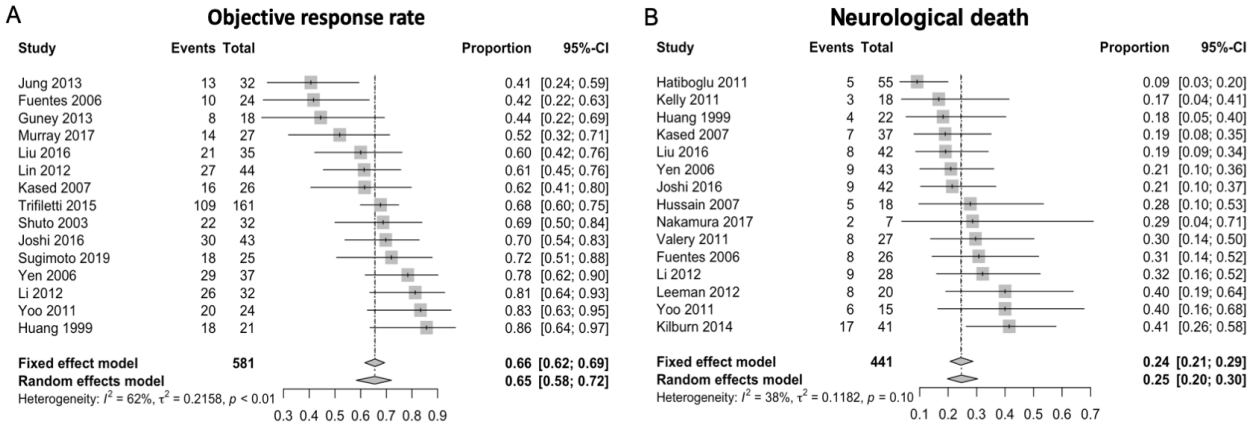
eFigure 2. Funnel plots for publication bias

Funnel plots are shown for endpoints examined across BSM studies. P-values shown are from Egger's regression test for funnel plot symmetry. All P-values are >0.05, indicating no statistically significant publication bias was identified in this study.



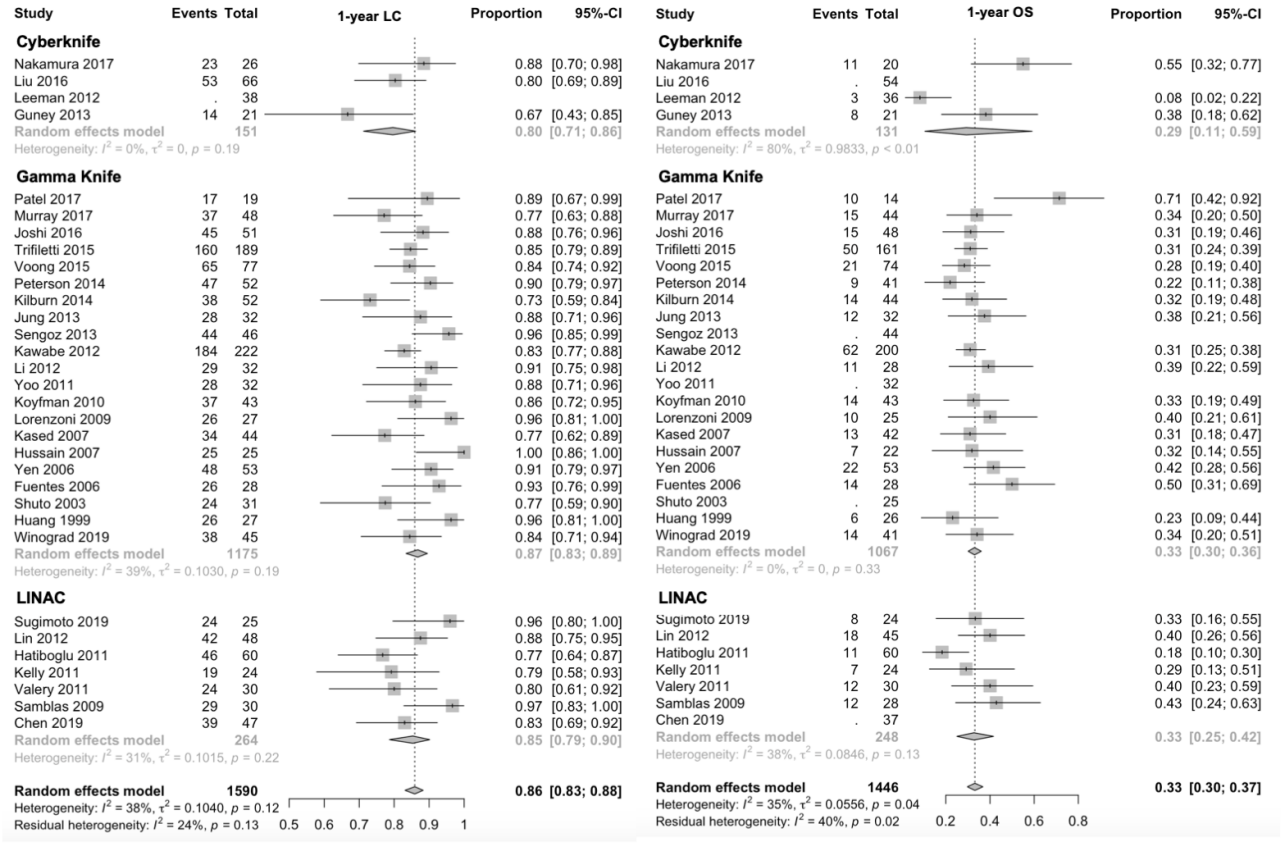
eFigure 3. Heterogeneity after excluding outlier BSM studies

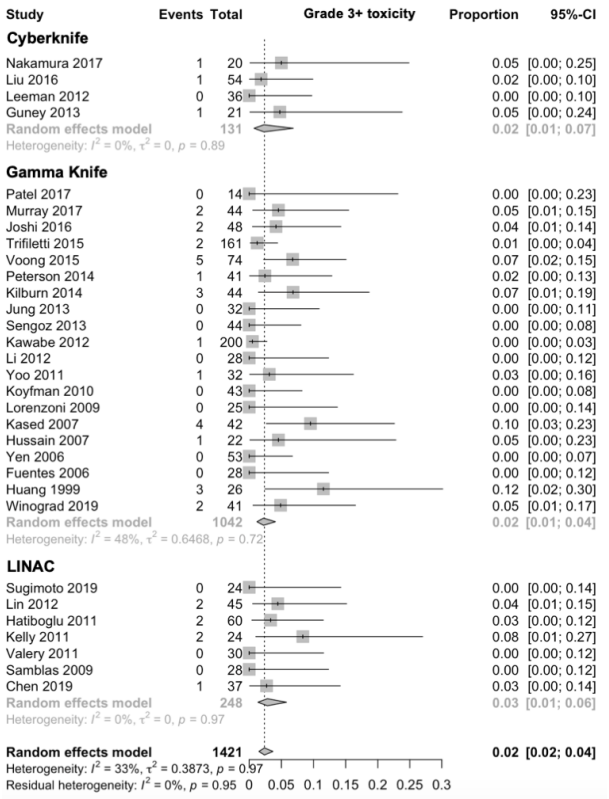
There was evidence for significant heterogeneity (I^2>50%) for ORR and neurological death. Outlier influential study analysis was performed and outlier studies (N=2 in each case; Samblas et al and Kawabe et al for neurological death, and Samblas et al and Koyfman et al for ORR) were identified using the Cook's distance method, and pooled meta-analysis was re-performed excluding these studies. Heterogeneity was reduced in each case, but the resulting pooled estimates were not substantially changed. Thus, study heterogeneity did not influence the conclusions of this meta-analysis.

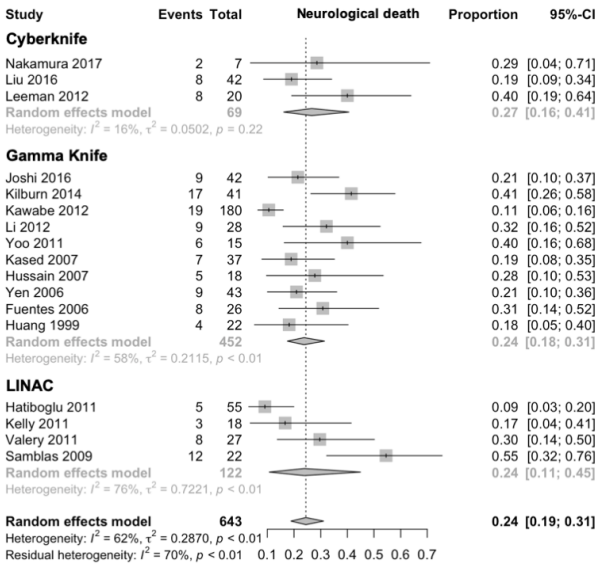


eFigure 4. Outcomes grouped by radiation modality

Pooled outcomes are shown grouped by radiation modality: Gamma Knife SRS, Cyberknife SRS, and linear accelerator (LINAC) SRS.

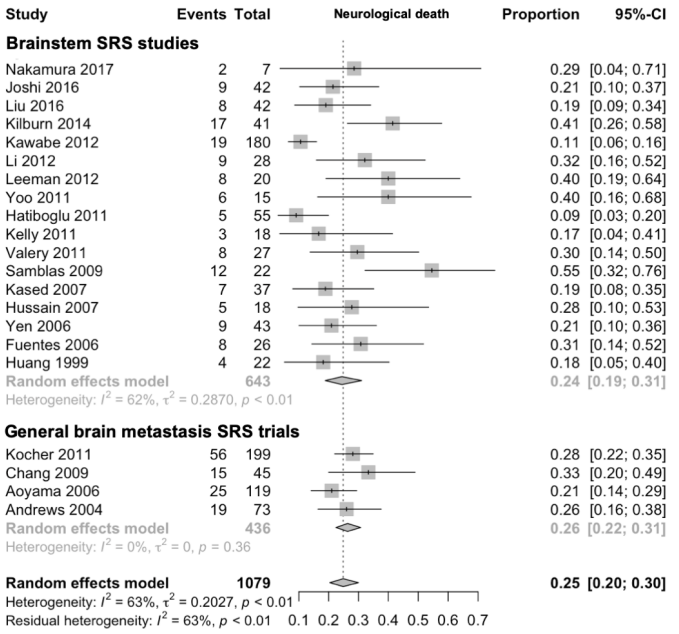


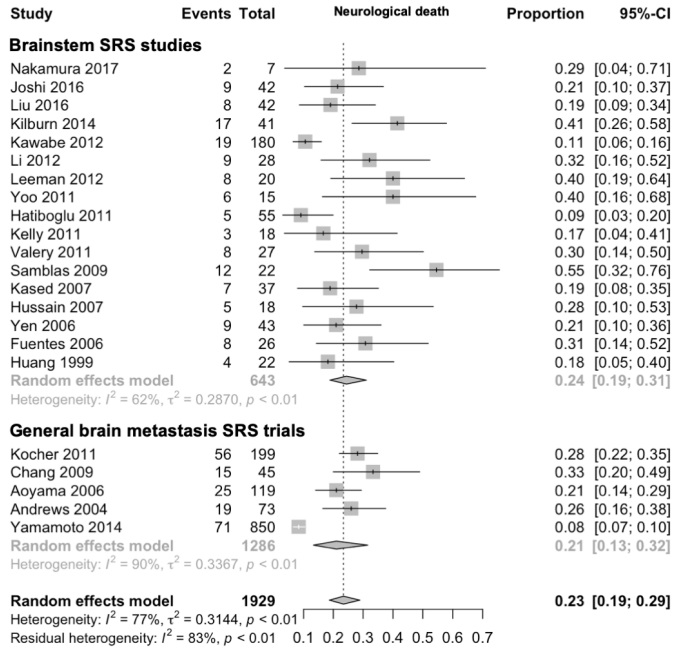




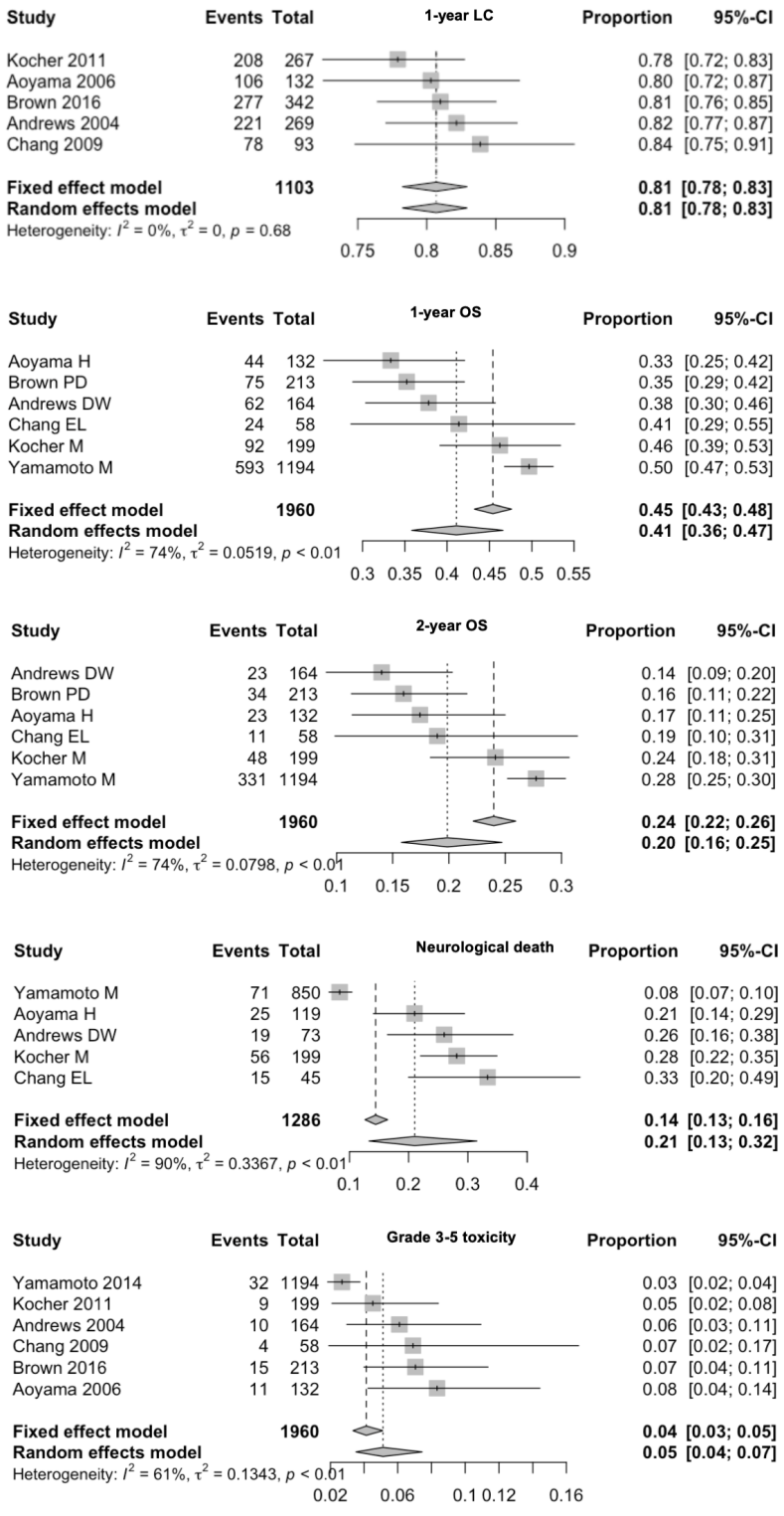
eFigure 5. Pooled neurologic death rate of BSM studies and BM trials

Pooled comparison of neurologic death rate between BSM studies and BM trials are shown, both including (bottom) Yamamoto et al, which reported an outlier neurologic death of 8%, and excluding excluding Yamamoto et al (top). Test for subgroup differences as a moderator in a random effects model between BSM studies and BM trials were non-significant in both cases (Q=0.11, P=0.74 for full dataset, Q=0.87, P=0.35 excluding Yamamoto et al).



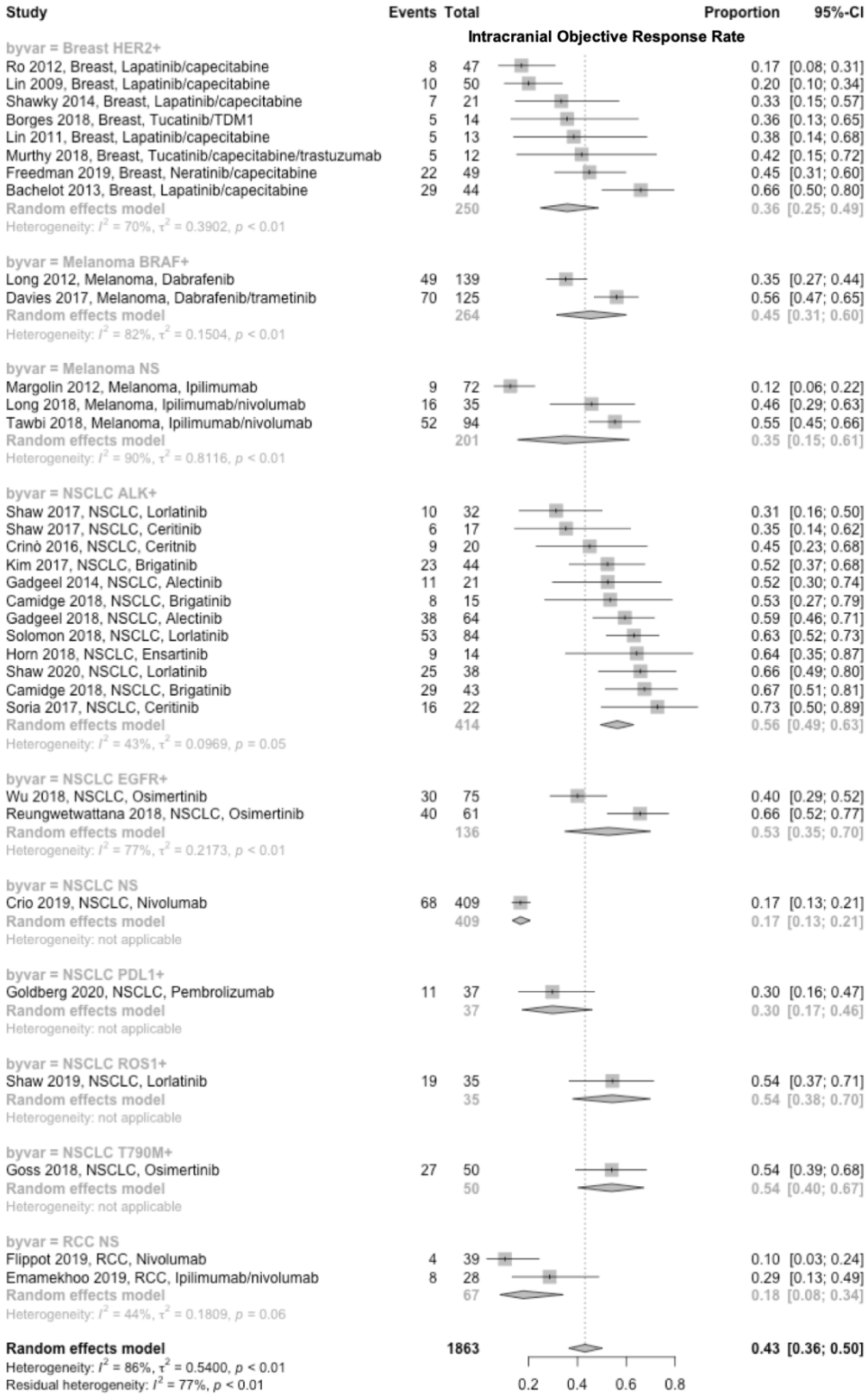


eFigure 6. Pooled outcomes for BM SRS trials.

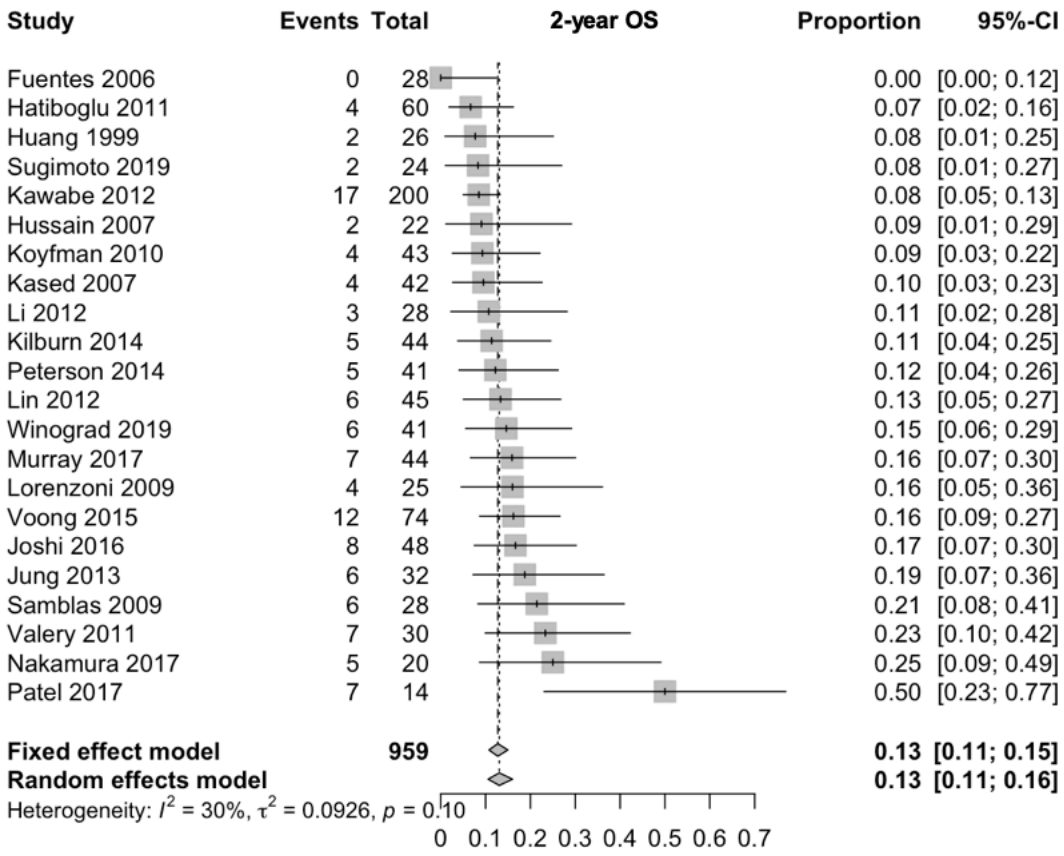


eFigure 7. Forest plot of intracranial response rates for central-nervous system penetrant targeted and immunotherapies

Forest plots and pooled estimates of published prospective trial reporting intracranial brain metastasis objective response rates (ORR) for targeted or immunotherapies, grouped by disease site and drug target, if applicable. Studies demonstrating no central-nervous-system (CNS) activity (ORR < 10%) were not included in the quantitative pooled analysis. Study level characteristics and references are reported in Supplement 5.



eFigure 8. Two-year overall survival for BSM studies



eTable 1. Univariate meta-regression P-values of study level characteristics in relation to outcomes of interest.

Variable (N studies, range of values)	1y LC	1y OS	2y OS	ORR	Sx response	G3-5 tox	Neuro death
Median age (N=31, 50-69)	0.700	0.263	0.159	**0.050**$^{+}$	**0.001**$^{+}$	0.454	**0.048**$^{-}$
Male % (N=31, 36-72%)	0.386	0.951	*0.079*$^{-}$	*0.064*$^{+}$	0.981	0.273	0.927
RPA 1 % (N=15, 0-20%)	0.302	0.782	*0.084*$^{+}$	0.657	0.677	0.564	0.587
RPA 2 % (N=15, 31-86%)	*0.055*$^{-}$	0.166	*0.099*$^{-}$	0.788	0.470	0.648	0.351
RPA 3 % (N=15, 0-50%)	0.170	0.149	0.320	0.564	0.382	0.802	0.574
Symptomatic % (N=22, 4-100%)	0.527	0.751	0.657	**0.024**$^{-}$	0.980	0.416	**0.037**$^{+}$
Solitary met % (N=29, 11-73%)	0.210	0.733	0.346	0.237	0.874	0.653	0.735
WBRT % (N=30, 0-100%)	0.920	0.809	0.200	**0.022**$^{-}$	0.237	**0.046**$^{+}$	0.364
Lung % (N=31, 29-79%)	**0.034**$^{+}$	0.462	0.636	0.152	0.633	**0.020**$^{-}$	0.376
Melanoma % (N=31, 0-31%)	0.297	0.787	0.661	0.552	0.714	**0.042**$^{+}$	0.408
Renal % (N=31, 0-21%)	0.599	0.315	0.589	0.499	0.501	0.499	0.255
BSM volume (N=31, 0.04-2.82)	0.874	0.222	0.944	0.436	0.956	0.212	0.234
BED10 margin (N=31, 23.5-60Gy)	0.299	0.980	**0.016**$^{-}$	**0.040**$^{+}$	*0.061*$^{+}$	0.141	0.439
BED10 max - calc (N=28, 27.9-237.6Gy)	*0.080*$^{+}$	0.193	0.279	**0.039**$^{+}$	0.363	0.473	0.939
RT Modality (subgroup comparison)	0.162	0.962	Insuff*	0.348	0.809	0.881	0.921

P-values are shown, with statistically significant results bolded, and trend P-values ≤ 0.10 in italics.

+, positive regression coefficient indicating positive correlation of variable with outcome.

-, negative regression coefficient indicating negative correlation of variable with outcome.

* insufficient number of studies with reported outcome across subgroups to perform comparison. Subgroups were compared by estimating between-subgroup-effects using a random effects model.

Abbreviations: BED10, biological effective dose with alpha/beta ratio = 10; G3-5 tox, grade 3-5 toxicity; LC, local control; ORR, objective response rate (complete or partial response); OS,

overall survival; RPA, recursive partitioning analysis; RT, radiotherapy; Sx, symptom; tox, toxicity

eTable 2. Characteristics of published trials of SRS for non-brainstem intracranial metastases.

Author/year	Years of tx	Excluded brainstem	N pts/N BM	Median age (range)	RPA I/II/III	Lung	Breast	Renal	Melanoma	Solitary brain met	WBRT	1y LC	1y OS	2y OS	Neuro death	G3-5 tox
Brown 2016	2002-2013	Yes	213/342	60.6 (NR)	NR/NR/NR	68.5%	8.5%	3.3%	5.6%	52.1%	47.9%	80.9%	35.0%	16.0%	NR	7.0%
Yamamoto 2014	2009-2012	No	1194/NR	65.8 (30-91)	28%/68.6%/5.7%	76.4%	10.3%	3.0%	NR	38.1%	0.0%	87.0%	49.7%	27.7%	8.4%	2.7%
Kocher 2011	1996-2007	Yes	199/267	60 (26-81)	NR/NR/NR	53.0%	12.0%	8.0%	5.0%	62.3%	47.7%	78.0%*	46.0%	24.0%	35.8%**	4.5%**
Chang 2009	2001-2007	Unclear	58/93	63.5 (NR)	17.2%/82.8%/0%	55.2%	13.8%	6.9%	12.1%	56.8%	48.3%	83.5%*	42.0%	18.8%	33.3%	6.9%
Aoyama 2006	1999-2003	Unclear	132/NR	62.3 (33-86)	14.4%/85.6%/0%	66.7%	6.8%	7.6%	0.0%	48.5%	49.2%	80.6%*	33.5%	17.5%	21.0%	8.3%
Andrews 2004	1996-2001	Yes	164/269	58.8 (19-82)	28%/72%/0%	64.0%	9.0%	1.0%	4.0%	56.0%	100.0%	82.0%	38.0%	14.0%	26.0%	6.1%

Abbreviations: BM, brain metastases; BSM, brainstem metastases; CPA, cerebello-pontine angle; CR, complete response; f/u, follow up; fx, fractions; G3-5 tox, grade 3-5 toxicity; GI, gastrointestinal; GPA, graded prognostic assessment; IQR, interquartile range; LC, local control; NR, not reported; OS, overall survival; RPA, recursive partitioning analysis; tx, treatment; WBRT, whole brain radiotherapy.

*1-year LC was estimated by extrapolating the median between 1-year LC of stereotactic radiosurgery alone and stereotactic radiosurgery plus whole-brain radiation arms, given the balanced numbers of patients within each arm.

**Due to aggregation of surgery and radiosurgery patients, G3-5 toxicity for SRS was estimated based on the narrative "serious adverse event form" results reported in the article, with N=9 events attributable to SRS and not disease progression or surgery. Neurological death was estimated by extrapolating the median rate between arms, given the balanced arms. The number of deaths overall and due to neurologic causes among SRS patients (N=58 of 162) was assumed to be proportional to the number of patients receiving SRS in the whole cohort, as subset analyses by the authors identified no difference in mortality based upon receipt of SRS versus surgery.

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