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

eMethods

eFigure 1. PRISMA Flowcharts

eFigure 2. Funnel Plots for Publication Bias

eFigure 3. Heterogeneity After Excluding Outlier BSM Studies

eFigure 4. Outcomes Grouped by Radiation Modality

eFigure 5. Pooled Neurologic Death Rate of BSM Studies and BM Trials

eFigure 6. Pooled Outcomes for BM SRS Trials

eFigure 7. Forest Plot of Intracranial Response Rates for Central-Nervous System Penetrant Targeted and Immunotherapies

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

eTable 2. Characteristics of Published Trials of SRS for Non-Brainstem Intracranial Metastases

eReferences

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 formula¹. 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 Sheet². 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 \geq 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) criteria³, and Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines were followed⁴.

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.

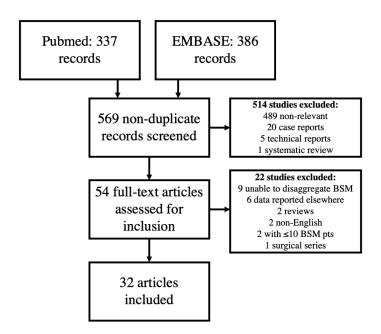
Publication bias was assessed with funnel plots of sample size rather than standard error versus treatment effect when proportions tended to the extreme (>80% and <20%), as the standard error can be biased in meta-analysis of proportions when proportions are close to an extreme⁵. Publication bias was tested via Egger's regression test using the *regtest* function within the *metafor* package in R.

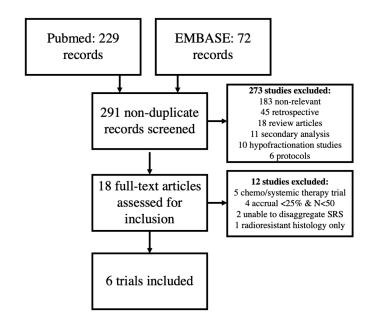
Most studies ascribed neurologic death based upon criteria previously established by Patchell et al⁶, scoring events when patients died of progressive neurologic dysfunction from brain metastases and/or leptomeningeal disease, or when patients had evidence of severe neurologic dysfunction at time of 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).

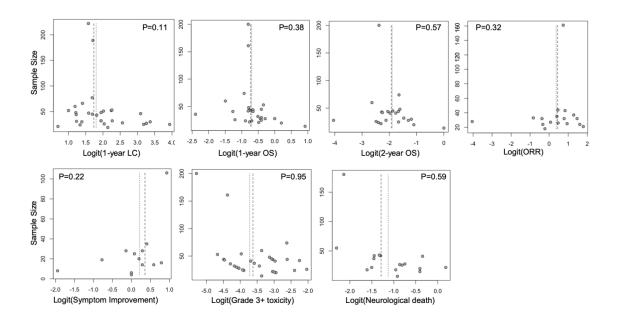
A)





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 ($l^2 > 50\%$) 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.

А	Objective	response rate			В	Ne	urological death	
Study	Events Total		Proportion	95%-CI	Study	Events	Total	Proportion 95%-Cl
Jung 2013 Fuentes 2006 Guney 2013 Murray 2017 Liu 2016 Lin 2012 Kased 2007 Trifiletti 2015 Shuto 2003 Joshi 2016 Sugimoto 2019 Yen 2006 Li 2012 Yoo 2011 Huang 1999 Fixed effect model Random effects model			0.42 0.44 0.52 0.60 0.61 0.62 0.68 0.69 0.70 0.72 0.78 0.81 0.83 0.86	[0.24; 0.59] [0.22; 0.63] [0.32; 0.71] [0.42; 0.76] [0.45; 0.76] [0.40; 0.75] [0.50; 0.84] [0.51; 0.88] [0.51; 0.88] [0.51; 0.83] [0.62; 0.90] [0.64; 0.93] [0.64; 0.97] [0.62; 0.69] [0.65; 0.72]	Hatiboglu 2011 Kelly 2011 Huang 1999 Kased 2007 Liu 2016 Yen 2006 Joshi 2016 Hussain 2007 Nakamura 2017 Valery 2011 Fuentes 2006 Li 2012 Leeman 2012 Yoo 2011 Kilburn 2014 Fixed effect model Random effects model		55 - 18 - 22 - 37 - 43 - 43 - 43 - 7 - 26 - 27 - 28 - 20 - 15 - 41 -	0.09 [0.03; 0.20] 0.17 [0.04; 0.41] 0.18 [0.05; 0.40] 0.19 [0.08; 0.35] 0.19 [0.08; 0.35] 0.21 [0.10; 0.36] 0.21 [0.10; 0.37] 0.28 [0.10; 0.53] 0.29 [0.04; 0.71] 0.30 [0.14; 0.50] 0.31 [0.14; 0.52] 0.32 [0.16; 0.52] 0.40 [0.19; 0.64] 0.40 [0.19; 0.64] 0.41 [0.26; 0.58] 0.24 [0.21; 0.29] 0.25 [0.20; 0.30]
Heterogeneity: I ² = 62%		0.4 0.5 0.6 0.7 0.8 0.9			Heterogeneity: I ² = 38%	%, τ ² = 0.1182,	, p = 0.10 0.1 0.2 0.3 0.4 0.5 (0.6 0.7

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.

Study	Events Total	1-year LC Pro	portion 95%-	CI Study	Events Total	1-year OS	Proportion 95%-Cl
Cyberknife		:		Cyberknife		:	
Nakamura 2017	23 26		0.88 [0.70; 0.9		11 20		0.55 [0.32; 0.77]
Liu 2016	53 66		0.80 [0.69; 0.8		. 54	_	0.00 [0.02, 0.11]
Leeman 2012	. 38	_	[,	Leeman 2012	3 36	_	0.08 [0.02; 0.22]
Guney 2013	14 21		0.67 [0.43; 0.8	5] Guney 2013	8 21		0.38 [0.18; 0.62]
Random effects mod			0.80 [0.71; 0.8				0.29 [0.11; 0.59]
Heterogeneity: $I^2 = 0\%$,	$\tau^2 = 0, p = 0.19$			Heterogeneity: $I^2 = 8$	0%, $\tau^2 = 0.9833$, $p < 0.01$		
Gamma Knife				Gamma Knife			
Patel 2017	17 19		0.89 [0.67; 0.9	9] Patel 2017	10 14		0.71 [0.42; 0.92]
Murray 2017	37 48		0.77 [0.63; 0.8	8] Murray 2017	15 44		0.34 [0.20; 0.50]
Joshi 2016	45 51		0.88 [0.76; 0.9		15 48		0.31 [0.19; 0.46]
Trifiletti 2015	160 189		0.85 [0.79; 0.8		50 161		0.31 [0.24; 0.39]
Voong 2015	65 77		0.84 [0.74; 0.9		21 74		0.28 [0.19; 0.40]
Peterson 2014	47 52		0.90 [0.79; 0.9		9 41 —		0.22 [0.11; 0.38]
Kilburn 2014	38 52		0.73 [0.59; 0.8		14 44		0.32 [0.19; 0.48]
Jung 2013	28 32		0.88 [0.71; 0.9		12 32		0.38 [0.21; 0.56]
Sengoz 2013	44 46		0.96 [0.85; 0.9		. 44 62 200	-	0.21 (0.25: 0.28)
Kawabe 2012 Li 2012	184 222 29 32		0.83 [0.77; 0.8	-,	11 28		0.31 [0.25; 0.38] 0.39 [0.22; 0.59]
Yoo 2011	29 32 28 32		0.91 [0.75; 0.9 0.88 [0.71; 0.9		. 32		0.39 [0.22, 0.39]
Kovfman 2010	37 43		0.86 [0.72; 0.9		14 43		0.33 [0.19; 0.49]
Lorenzoni 2009	26 27		0.96 [0.81; 1.0	-, ,	10 25		0.40 [0.21; 0.61]
Kased 2007	34 44		0.77 [0.62; 0.8		13 42	-	0.31 [0.18; 0.47]
Hussain 2007	25 25		1.00 [0.86; 1.0		7 22 -	-	0.32 [0.14; 0.55]
Yen 2006	48 53		0.91 [0.79; 0.9	7] Yen 2006	22 53		0.42 [0.28; 0.56]
Fuentes 2006	26 28		0.93 [0.76; 0.9		14 28	-	0.50 [0.31; 0.69]
Shuto 2003	24 31		0.77 [0.59; 0.9		. 25	_	
Huang 1999	26 27		0.96 [0.81; 1.0		6 26 —		0.23 [0.09; 0.44]
Winograd 2019	38 45		0.84 [0.71; 0.9		14 41		0.34 [0.20; 0.51]
Random effects mod		♦	0.87 [0.83; 0.8	9] Random effects m Heterogeneity: I ² = 0		Q	0.33 [0.30; 0.36]
Heterogeneity: $I^2 = 39\%$	$\delta, \tau^2 = 0.1030, p = 0.19$			0 ,	$\%, \tau^{-} = 0, \rho = 0.33$		
LINAC				LINAC			
Sugimoto 2019	24 25		0.96 [0.80; 1.0		8 24 -		0.33 [0.16; 0.55]
Lin 2012	42 48		0.88 [0.75; 0.9		18 45		0.40 [0.26; 0.56]
Hatiboglu 2011	46 60		0.77 [0.64; 0.8		11 60 —	-	0.18 [0.10; 0.30]
Kelly 2011	19 24		0.79 [0.58; 0.9		7 24 -		0.29 [0.13; 0.51]
Valery 2011	24 30		0.80 [0.61; 0.9		12 30 12 28		0.40 [0.23; 0.59] 0.43 [0.24; 0.63]
Samblas 2009	29 30 39 47		0.97 [0.83; 1.0		12 28		0.43 [0.24; 0.63]
Chen 2019 Random effects mod			0.83 [0.69; 0.9	-		-	0.33 [0.25; 0.42]
Heterogeneity: $I^2 = 31\%$			0.85 [0.79; 0.9		$8\%, \tau^2 = 0.0846, p = 0.13$		0.00 [0.20, 0.42]
Herefogeneity: $T = 31\%$	ο, τ = 0.1015, μ = 0.22						
Random effects mod	del 1590	\$	0.86 [0.83; 0.8	Random effects m		÷	0.33 [0.30; 0.37]
Heterogeneity: $I^2 = 38\%$			2.00 [0.00, 0.0	Heterogeneity: $I^2 = 3$	5%, $\tau^2 = 0.0556$, $p = 0.04$		1
	$I^2 = 24\%, p = 0.13$ 0.5	0.6 0.7 0.8 0.9 1		Residual heterogene	ity: $I^2 = 40\%$, $p = 0.02$	0.2 0.4 0.6 0	0.8

Study	Events Total	ORR	Proportion 95%-CI	Study	Events Total	Symptom Improvement	Proportion 95%-CI
Cyberknife		:		Cyberknife			
Liu 2016 Guney 2013 Random effects mod Heterogeneity: / ² = 0%.			0.60 [0.42; 0.76] 0.44 [0.22; 0.69] 0.55 [0.41; 0.67]	Guney 2013 Random effects mod Heterogeneity: not appl			0.55 [0.32; 0.77] 0.55 [0.34; 0.75]
5	, t = 0, p = 0.20			Gamma Knife			
Gamma Knife Murray 2017 Joshi 2016 Trifiletti 2015 Jung 2013 Li 2012 Yoo 2011 Koyfman 2010 Kased 2007 Yen 2006 Fuentes 2006 Shuto 2003	$\begin{array}{cccccccccccccccccccccccccccccccccccc$		0.52 [0.32; 0.71] 0.70 [0.54; 0.83] 0.68 [0.60; 0.75] 0.41 [0.24; 0.59] 0.83 [0.63; 0.95] 0.30 [0.16; 0.49] 0.62 [0.41; 0.80] 0.78 [0.62; 0.90] 0.42 [0.22; 0.63] 0.69 [0.50; 0.84]	Joshi 2016 Triflietti 2015 Jung 2013 Kased 2007 Yen 2006 Fuentes 2006 Huang 1999 Winograd 2019 Random effects mor- heterogeneity: <i>I</i> ² = 599 LINAC			$\begin{array}{cccc} 0.69 & [0.41; 0.89] \\ 0.72 & [0.62; 0.80] \\ 0.32 & [0.13; 0.57] \\ 0.12 & [0.00; 0.53] \\ 0.60 & [0.42; 0.76] \\ 0.57 & [0.37; 0.76] \\ 0.52 & [0.31; 0.72] \\ 0.64 & [0.35; 0.87] \\ 0.56 & [0.44; 0.67] \end{array}$
Huang 1999 Random effects mod Heterogeneity: / ² = 79% LINAC	$\begin{array}{c cccc} & & 18 & & 21 \\ \hline \mathbf{del} & & 492 \\ \%, \ \tau^2 = 0.4745, \ p < 0.01 \end{array}$	\sim	- 0.86 [0.64; 0.97] 0.65 [0.54; 0.74]	Sugimoto 2019 Kelly 2011 Valery 2011 Samblas 2009 Random effects mod			- 0.50 [0.12; 0.88] - 0.50 [0.07; 0.93] 0.57 [0.29; 0.82] 0.46 [0.28; 0.66] 0.50 [0.37; 0.63]
Sugimoto 2019 Lin 2012 Samblas 2009 Random effects mod Heterogeneity: / ² = 97%	%, $\tau^2 = 7.8213$, $p = 0.67$		0.72 [0.51; 0.88] 0.61 [0.45; 0.76] 0.00 [0.00; 0.12] 0.24 [0.01; 0.91]	Heterogeneity: $l^2 = 0\%$, Random effects mo Heterogeneity: $l^2 = 41\%$ Residual heterogeneity	del 323 %, τ ² = 0.1358, <i>ρ</i> = 0.06	0.2 0.4 0.6 0.8	0.55 [0.47; 0.63]
Random effects mod Heterogeneity: $I^2 = 88\%$ Residual heterogeneity:	%, $\tau^2 = 0.9805$, $p < 0.01$	0.4 0.6 0.8	0.59 [0.47; 0.71]				

Study	Events Total	Grade 3+ toxicity Proportion	95%-CI	Study	Events Total	Neurological death	Proportion	95%-CI
Cyberknife				Cyberknife				
Nakamura 2017 Liu 2016 Leeman 2012 Guney 2013 Random effects model Heterogeneity: / ² = 0%, r ² =	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	0.02 0.00 0.05	[0.00; 0.25] [0.00; 0.10] [0.00; 0.10] [0.00; 0.24] [0.01; 0.07]	Nakamura 2017 Liu 2016 Leeman 2012 Random effects mode Heterogeneity: $l^2 = 16\%$,		*	0.19 0.40	[0.04; 0.71] [0.09; 0.34] [0.19; 0.64] [0.16; 0.41]
	- 0, p = 0.03			Gamma Knife				
Gamma Knife Patel 2017 Murray 2017 Joshi 2016 Trifiletti 2015 Voong 2015 Peterson 2014 Kilburn 2014 Jung 2013 Sengoz 2013 Kawabe 2012 Li 2012 Yoo 2011 Koyfman 2010 Lorenzoni 2009 Kased 2007 Hussain 2007 Yen 2006 Fuentes 2006 Huang 1999 Winograd 2019 Random effects model Hetersoenety. $r^2 = 48\%$, r^2	0 14 2 44 2 161 5 74 1 41 3 44 0 32 0 44 1 200 0 28 1 32 0 43 0 25 4 42 1 22 0 53 0 28 3 26 2 41 0 28 0 28	0.05 0.04 0.01 0.07 0.02 0.07 0.02 0.07 0.02 0.07 0.07 0.07 0.07 0.00 0.012 0.02 0.03		Joshi 2016 Kilburn 2014 Kawabe 2012 Li 2012 Yoo 2011 Kased 2007 Hussain 2007 Yen 2006 Fuentes 2006 Huang 1999 Random effects mode Heterogeneity: l^2 = 58%. LINAC Hatiboglu 2011 Kelly 2011 Valery 2011 Samblas 2009 Random effects mode Heterogeneity: l^2 = 67%.	9 28 6 15 7 37 5 18 9 43 8 26 4 22 $t^2 = 0.2115, p < 0.01$ 5 55 8 27 12 22 $t^2 = 0.7221, p < 0.01$ 122 $t^2 = 0.7221, p < 0.01$		0.41 0.11 0.32 0.40 0.19 0.28 0.21 0.31 0.31 0.24 0.09 0.17 0.30 - 0.55 0.24	[0.10; 0.37] [0.26; 0.58] [0.06; 0.16] [0.16; 0.52] [0.16; 0.68] [0.03; 0.35] [0.10; 0.53] [0.10; 0.36] [0.10; 0.36] [0.14; 0.52] [0.52; 0.40] [0.52; 0.40] [0.03; 0.20] [0.04; 0.41] [0.14; 0.50] [0.32; 0.76] [0.11; 0.45]
LINAC				Residual heterogeneity: I	² = 70%, <i>p</i> < 0.01 C	0.1 0.2 0.3 0.4 0.5 0.6 0.7		
Sugimoto 2019 Lin 2012 Hatiboglu 2011 Kelly 2011 Valery 2011 Samblas 2009 Chen 2019 Random effects model Heterogeneity: $l^2 = 0\%, \tau^2$ =	0 24 - 2 45 - 2 24 - 0 30 - 1 37 - 248	0.04 0.03 0.03 0.08 0.00 0.00 0.00 0.00 0.03	[0.00; 0.14] [0.01; 0.15] [0.00; 0.12] [0.01; 0.27] [0.00; 0.12] [0.00; 0.12] [0.00; 0.14] [0.01; 0.06]					
Random effects model Heterogeneity: $I^2 = 33\%$, τ^2 Residual heterogeneity: $I^2 =$		0.02 5 0.1 0.15 0.2 0.25 0.3	[0.02; 0.04]					

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).

Study	Events [·]	Total	Neurological death	Proportion	95%-CI
Brainstem SRS stu	dies				
Nakamura 2017	2	7		0.29	[0.04; 0.71]
Joshi 2016	9	42			[0.10; 0.37]
Liu 2016	8	42		0.19	[0.09; 0.34]
Kilburn 2014	17	41		0.41	[0.26; 0.58]
Kawabe 2012	19	180		0.11	[0.06; 0.16]
Li 2012	9	28			[0.16; 0.52]
Leeman 2012	8	20			[0.19; 0.64]
Yoo 2011	6	15			[0.16; 0.68]
Hatiboglu 2011	5	55			[0.03; 0.20]
Kelly 2011	3	18			[0.04; 0.41]
Valery 2011	8	27			[0.14; 0.50]
Samblas 2009 Kased 2007	12 7	22 37			[0.32; 0.76]
Kased 2007 Hussain 2007	5	37 18			[0.08; 0.35] [0.10; 0.53]
Yen 2006	9	43			[0.10; 0.33]
Fuentes 2006	8	26			[0.14; 0.52]
Huang 1999	4	22			[0.05; 0.40]
Random effects mode		643			[0.19; 0.31]
Heterogeneity: $I^2 = 62\%$,			01	0124	[0.10, 0.01]
General brain meta	stasis SF	RS tria	als		
Kocher 2011	56	199		0.28	[0.22; 0.35]
Chang 2009	15	45			[0.20; 0.49]
Aoyama 2006	25	119		0.21	[0.14; 0.29]
Andrews 2004	19	73		0.26	[0.16; 0.38]
Random effects mode		436	\sim	0.26	[0.22; 0.31]
Heterogeneity: $I^2 = 0\%$, τ^2	$p^2 = 0, p = 0.$	36			
Random effects mode		1079	\diamond	0.25	[0.20; 0.30]
Heterogeneity: I ² = 63%,					
Residual heterogeneity: /	² = 63%, p <	< 0.01	0.1 0.2 0.3 0.4 0.5 0.6 0.7		

Study	Events Tot	Neurological death	Proportion 95%-CI			
Brainstem SRS s	tudies	:				
Nakamura 2017	2	7	0.29 [0.04; 0.71]			
Joshi 2016	9 4	2	0.21 [0.10; 0.37]			
Liu 2016		2	0.19 [0.09; 0.34]			
Kilburn 2014		1	0.41 [0.26; 0.58]			
Kawabe 2012	19 18		0.11 [0.06; 0.16]			
Li 2012		8	0.32 [0.16; 0.52]			
Leeman 2012		0 •	0.40 [0.19; 0.64]			
Yoo 2011		5 •	0.40 [0.16; 0.68]			
Hatiboglu 2011		5	0.09 [0.03; 0.20]			
Kelly 2011		8	0.17 [0.04; 0.41]			
Valery 2011		7	0.30 [0.14; 0.50]			
Samblas 2009		2 *	- 0.55 [0.32; 0.76]			
Kased 2007 Hussain 2007		7	0.19 [0.08; 0.35]			
Yen 2006		3	0.28 [0.10; 0.53] 0.21 [0.10; 0.36]			
Fuentes 2006		6	0.31 [0.14; 0.52]			
Huang 1999		2	0.18 [0.05; 0.40]			
Random effects mo			0.24 [0.19; 0.31]			
Heterogeneity: $I^2 = 629$			0.24 [0.13, 0.01]			
General brain me	tastasis SRS	rials				
Kocher 2011	56 19	9 + -	0.28 [0.22; 0.35]			
Chang 2009	15 4	5	0.33 [0.20; 0.49]			
Aoyama 2006	25 11	9	0.21 [0.14; 0.29]			
Andrews 2004	19 7	3	0.26 [0.16; 0.38]			
Yamamoto 2014	71 85		0.08 [0.07; 0.10]			
Random effects mo			0.21 [0.13; 0.32]			
Heterogeneity: $I^2 = 90$	%, τ ² = 0.3367, <i>p</i> <	0.01				
Random effects model 1929 0.23 [0.19; 0.29] Heterogeneity: $l^2 = 77\%$, $\tau^2 = 0.3144$, $p < 0.01$ 0.23 [0.19; 0.29] Residual heterogeneity: $l^2 = 83\%$, $p < 0.01$ 0.1 0.2 0.3 0.4 0.5 0.6 0.7						

© 2021 American Medical Association. All rights reserved.

eFigure 6. Pooled outcomes for BM SRS trials.

Study	Events Total	1-year LC	Proportion 95%-CI
Kocher 2011 Aoyama 2006 Brown 2016 Andrews 2004 Chang 2009	2082671061322773422212697893		0.78 [0.72; 0.83] 0.80 [0.72; 0.87] 0.81 [0.76; 0.85] 0.82 [0.77; 0.87] 0.84 [0.75; 0.91]
Fixed effect model Random effects mod Heterogeneity: $I^2 = 0\%$, γ		0.75 0.8 0.85	0.81 [0.78; 0.83] 0.81 [0.78; 0.83] 0.9

Study	Events	Total	1-year OS	Proportion	95%-CI
Aoyama H Brown PD Andrews DW Chang EL Kocher M Yamamoto M	44 75 62 24 92 593	132 213 164 58 199 1194		0.35 0.38 0.41 0.46	[0.25; 0.42] [0.29; 0.42] [0.30; 0.46] [0.29; 0.55] [0.39; 0.53] [0.47; 0.53]
Fixed effect model Random effects mod Heterogeneity: $I^2 = 74\%$,		1960 9, <i>p</i> < 0.0		0.41	[0.43; 0.48] [0.36; 0.47]

Study	Events Total	2-year OS	Proportion 95%-CI
Andrews DW	23 164 —		0.14 [0.09; 0.20]
Brown PD	34 213		0.16 [0.11; 0.22]
Aoyama H	23 132		0.17 [0.11; 0.25]
Chang EL	11 58 —		- 0.19 [0.10; 0.31]
Kocher M	48 199		0.24 [0.18; 0.31]
Yamamoto M	331 1194		0.28 [0.25; 0.30]
Fixed effect model	1960	-	0.24 [0.22; 0.26]
Random effects mode			0.20 [0.16; 0.25]
Heterogeneity: $I^2 = 74\%$,	$\tau^2 = 0.0798, p < 0.01$		
	0.1	0.15 0.2 0.25 0.3	3

Study	Events Total	Neurological death	Proportion 95%-CI
Yamamoto M Aoyama H Andrews DW Kocher M	71 850 - 25 119 19 73 56 199		0.08 [0.07; 0.10] 0.21 [0.14; 0.29] 0.26 [0.16; 0.38] 0.28 [0.22; 0.35]
Chang EL	15 45		- 0.33 [0.20; 0.49]
Fixed effect model Random effects mode Heterogeneity: $I^2 = 90\%$, γ			0.14 [0.13; 0.16] 0.21 [0.13; 0.32]

Study	Events	Total	Grade 3-5 toxicity	Proportion	95%-CI
Yamamoto 2014	32	1194		0.03	[0.02; 0.04]
Kocher 2011	9	199		0.05	[0.02; 0.08]
Andrews 2004	10	164		0.06	[0.03; 0.11]
Chang 2009	4	58		0.07	[0.02; 0.17]
Brown 2016	15	213		0.07	[0.04; 0.11]
Aoyama 2006	11	132		0.08	[0.04; 0.14]
Fixed effect model Random effects mode	I	1960			[0.03; 0.05] [0.04; 0.07]
Heterogeneity: $I^2 = 61\%$, τ	r ² = 0.1343	B, p < 0	.01		
		0	.02 0.06 0.1 0.12 0.16	5	

© 2021 American Medical Association. All rights reserved.

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.

Study	Events	Total	Pro	portion	95%-CI
human = Broost UED2+		Int	racranial Objective Response R	ate	
byvar = Breast HER2+ Ro 2012, Breast, Lapatinib/capecitabine Lin 2009, Breast, Lapatinib/capecitabine Shawky 2014, Breast, Lapatinib/capecitabine	8 10 7	47 50 21		0.20	[0.08; 0.31] [0.10; 0.34] [0.15; 0.57]
Borges 2018, Breast, Tucatinib/TDM1 Lin 2011, Breast, Lapatinib/capecitabine	5 5	14 13		0.36 0.38	[0.13; 0.65] [0.14; 0.68]
Murthy 2018, Breast, Tucatinib/capecitabine/trastuzumab Freedman 2019, Breast, Neratinib/capecitabine Bachelot 2013, Breast, Lapatinib/capecitabine	5 22 29	12 49 44		0.45 0.66	[0.15; 0.72] [0.31; 0.60] [0.50; 0.80]
Random effects model Heterogeneity: $I^2 = 70\%$, $\tau^2 = 0.3902$, $p < 0.01$		250		0.36	[0.25; 0.49]
byvar = Melanoma BRAF+ Long 2012, Melanoma, Dabrafenib Davies 2017, Melanoma, Dabrafenib/trametinib	49 70	139 125			[0.27; 0.44] [0.47; 0.65]
Random effects model Heterogeneity: $l^2 = 82\%$, $\tau^2 = 0.1504$, $p < 0.01$	70	264			[0.31; 0.60]
byvar = Melanoma NS					
Margolin 2012, Melanoma, Ipilimumab Long 2018, Melanoma, Ipilimumab/nivolumab	9 16	72 35			[0.06; 0.22] [0.29; 0.63]
Tawbi 2018, Melanoma, Ipilimumab/nivolumab	52	94		0.55	[0.45; 0.66]
Random effects model Heterogeneity: $l^2 = 90\%$, $\tau^2 = 0.8116$, $p < 0.01$		201		0.35	[0.15; 0.61]
byvar = NSCLC ALK+ Shaw 2017, NSCLC, Lorlatinib	10	32		0.31	[0.16; 0.50]
Shaw 2017, NSCLC, Ceritinib	6	17		0.35	[0.14; 0.62]
Crinò 2016, NSCLC, Ceritnib Kim 2017, NSCLC, Brigatinib	9 23	20 44			[0.23; 0.68] [0.37: 0.68]
Gadgeel 2014, NSCLC, Alectinib	11	21		0.52	[0.30; 0.74]
Camidge 2018, NSCLC, Brigatinib Gadgeel 2018, NSCLC, Alectinib	8 38	15 64			[0.27; 0.79] [0.46; 0.71]
Solomon 2018, NSCLC, Lorlatinib	53	84		0.63	[0.52; 0.73]
Horn 2018, NSCLC, Ensartinib Shaw 2020, NSCLC, Lorlatinib	9 25	14 38			[0.35; 0.87] [0.49; 0.80]
Camidge 2018, NSCLC, Brigatinib	29	43	-	0.67	[0.51; 0.81]
Soria 2017, NSCLC, Ceritinib Random effects model	16	22 414	\diamond		[0.50; 0.89] [0.49; 0.63]
Heterogeneity: $l^2 = 43\%$, $\tau^2 = 0.0969$, $\rho = 0.05$					
byvar = NSCLC EGFR+ Wu 2018, NSCLC, Osimertinib	30	75	_	0.40	[0.29; 0.52]
Reungwetwattana 2018, NSCLC, Osimertinib	40	61		0.66	[0.52; 0.77]
Random effects model Heterogeneity: $I^2 = 77\%$, $\tau^2 = 0.2173$, $p < 0.01$		136		0.53	[0.35; 0.70]
byvar = NSCLC NS	60	400	-	0.47	10 42: 0 041
Crio 2019, NSCLC, Nivolumab Random effects model	68	409 409	#		[0.13; 0.21] [0.13; 0.21]
Heterogeneity: not applicable					
byvar = NSCLC PDL1+ Goldberg 2020, NSCLC, Pembrolizumab	11	37		0.30	[0.16; 0.47]
Random effects model		37	\sim		[0.17; 0.46]
Heterogeneity: not applicable					
byvar = NSCLC ROS1+ Shaw 2019, NSCLC, Lorlatinib	19	35		0.54	[0.37; 0.71]
Random effects model	10	35			[0.38; 0.70]
Heterogeneity: not applicable					
byvar = NSCLC T790M+ Goss 2018, NSCLC, Osimertinib	27	50	-	0.54	10 30: 0 681
Random effects model	21	50			[0.39; 0.68] [0.40; 0.67]
Heterogeneity: not applicable					
byvar = RCC NS Flippot 2019, RCC, Nivolumab	4	39		0.10	[0.03; 0.24]
Emamekhoo 2019, RCC, Ipilimumab/nivolumab	8	28		0.29	[0.13; 0.49]
Random effects model Heterogeneity: $I^2 = 44\%$, $\tau^2 = 0.1809$, $p = 0.06$		67	\sim	0.18	[0.08; 0.34]
Random effects model		1863	4	0.43	[0.36; 0.50]
Heterogeneity: $l^2 = 86\%$, $\tau^2 = 0.5400$, $p < 0.01$				0.40	[3122] 0130]
Residual heterogeneity: I ² = 77%, p < 0.01			0.2 0.4 0.6 0.8		

eFigure 8. Two-year overall survival for BSM studies

Study	Events	Total	2-year OS	Proportion	95%-CI
Fuentes 2006	0	28		0.00	[0.00; 0.12]
Hatiboglu 2011	4	60			[0.02; 0.16]
Huang 1999	2	26			[0.01; 0.25]
Sugimoto 2019	2	24			[0.01; 0.27]
Kawabe 2012	17	200		0.08	[0.05; 0.13]
Hussain 2007	2	22		0.09	[0.01; 0.29]
Koyfman 2010	4	43		0.09	[0.03; 0.22]
Kased 2007	4	42		0.10	[0.03; 0.23]
Li 2012	3	28		0.11	[0.02; 0.28]
Kilburn 2014	5	44		0.11	[0.04; 0.25]
Peterson 2014	5	41		0.12	[0.04; 0.26]
Lin 2012	6	45		0.13	[0.05; 0.27]
Winograd 2019	6	41		0.15	[0.06; 0.29]
Murray 2017	7	44		0.16	[0.07; 0.30]
Lorenzoni 2009	4	25		0.16	[0.05; 0.36]
Voong 2015	12	74		0.16	[0.09; 0.27]
Joshi 2016	8	48		0.17	[0.07; 0.30]
Jung 2013	6	32		0.19	[0.07; 0.36]
Samblas 2009	6	28			[0.08; 0.41]
Valery 2011	7	30			[0.10; 0.42]
Nakamura 2017	5	20			[0.09; 0.49]
Patel 2017	7	14		0.50	[0.23; 0.77]
Fixed effect model		959	÷.	0.13	[0.11; 0.15]
Random effects model			<u> </u>	0.13	[0.11; 0.16]
Heterogeneity: $I^2 = 30\%$, τ^2	= 0.0926	b, p = 0.			
		(0 0.1 0.2 0.3 0.4 0.5 0.6 0.7		

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	2y OS	ORR	Sx	G3-5	Neuro
		OS			response	tox	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-	0.080	0.193	0.279	0.039	0.363	0.473	0.939
237.6Gy)	+			+			
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

Author/y	Years	Excl	Ν	Media	RPA	Lu	Br	Re	Mela	Soli	WB	1y	1y	2y	Neu	G3-
ear	of tx	uded	pts/	n age	I/II/III	ng	eas	nal	noma	tary	RT	LC	OS	OS	ro	5
		brain	Ν	(range			t			brai					deat	tox
		stem	BM)						n					h	
										met						
Brown	2002-	Yes	213/	60.6	NR/NR/	68.	8.5	3.3	5.6%	52.1	47.	80.	35.	16.	NR	7.0
2016	2013		342	(NR)	NR	5%	%	%		%	9%	9%	0%	0%		%
Yamamo	2009-	No	1194	65.8	28%/68.6	76.	10.	3.0	NR	38.1	0.0	87.	49.	27.	8.4	2.7
to 2014	2012		/NR	(30-	%/5.7%	4%	3%	%		%	%	0%	7%	7%	%	%
				91)												
Kocher	1996-	Yes	199/	60	NR/NR/	53.	12.	8.0	5.0%	62.3	47.	78.	46.	24.	35.8	4.5
2011	2007		267	(26-	NR	0%	0%	%		%	7%	0%	0%	0%	%**	%*
				81)								*				*
Chang	2001-	Uncl	58/9	63.5	17.2%/82	55.	13.	6.9	12.1	56.8	48.	83.	42.	18.	33.3	6.9
2009	2007	ear	3	(NR)	.8%/0%	2%	8%	%	%	%	3%	5%	0%	8%	%	%
												*				
Aoyama	1999-	Uncl	132/	62.3	14.4%/85	66.	6.8	7.6	0.0%	48.5	49.	80.	33.	17.	21.0	8.3
2006	2003	ear	NR	(33-	.6%/0%	7%	%	%		%	2%	6%	5%	5%	%	%
				86)								*				
Andrews	1996-	Yes	164/	58.8	28%/72	64.	9.0	1.0	4.0%	56.0	100	82.	38.	14.	26.0	6.1
2004	2001		269	(19-	%/0%	0%	%	%		%	.0%	0%	0%	0%	%	%
				82)												

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

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.

eReferences:

1. Fowler JF. 21 Years of biologically effective dose. *Br J Radiol*. 2010. doi:10.1259/bjr/31372149

2. National Institute of Cancer. Targeted Cancer Therapies: Targeted Therapies Fact Sheet. https://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet.

3. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (Minors): Development and validation of a new instrument. *ANZ J Surg.* 2003. doi:10.1046/j.1445-2197.2003.02748.x

4. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: Elaboration and explanation. *BMJ*. 2015. doi:10.1136/bmj.g7647

5. Hunter JP, Saratzis A, Sutton AJ, Boucher RH, Sayers RD, Bown MJ. In metaanalyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. *J Clin Epidemiol*. 2014. doi:10.1016/j.jclinepi.2014.03.003

6. Patchell RA, Tibbs PA, Walsh JW, et al. A Randomized Trial of Surgery in the Treatment of Single Metastases to the Brain. *N Engl J Med.* 1990. doi:10.1056/nejm199002223220802