Resection for Recurrent Brain Metastases: A Systematic review and Meta-analysis

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Background

- There is recurrence at some point following initial resection or radiosurgery in about 50% of patients previously treated for brain metastases (BMs); yet, little is known about the optimal management of recurrent BMs.
- To better understand the management of recurrent brain metastases, we carried out a systematic review and meta-analysis to describe outcomes of craniotomy for recurrent BMs after resection or stereotactic radiosurgery, with particular attention to recurrence in the previous resection cavity.

Methods

- A literature search in Pubmed, Embase and Cochrane databases was conducted on November 1st, 2018.
- The resulting literature and relevant references were screened using Covidence by two independent authors (AH and FI) with discordance resolved by a third author (NL).
- Data were extracted on study, patient, disease and treatment characteristics. Study quality was assessed using the NewCastle-Ottawa Scale (NOS).
- Studies were grouped by initial local treatment strategy to compare resection after resection (RAR) vs. resection after stereotactic radiosurgery (RAS).
- Pooled analysis using random effects model was performed in R version 3.4.1 using the meta package.

Discussion

- Recurrent BMs are a relatively understudied topic in neurosurgery, with only two studies published to date offering guidelines for management.
- In this meta-analysis, a longer interval between initial treatment and craniotomy for recurrence was found to be associated with improved survival. Lung and gastrointestinal primary tumors were associated with poor survival outcomes.
- Local control, intracranial control and survival outcomes were similar regardless of initial treatment before recurrence.
- The small sample sizes of the individual studies warrant caution in interpreting the results.

Results

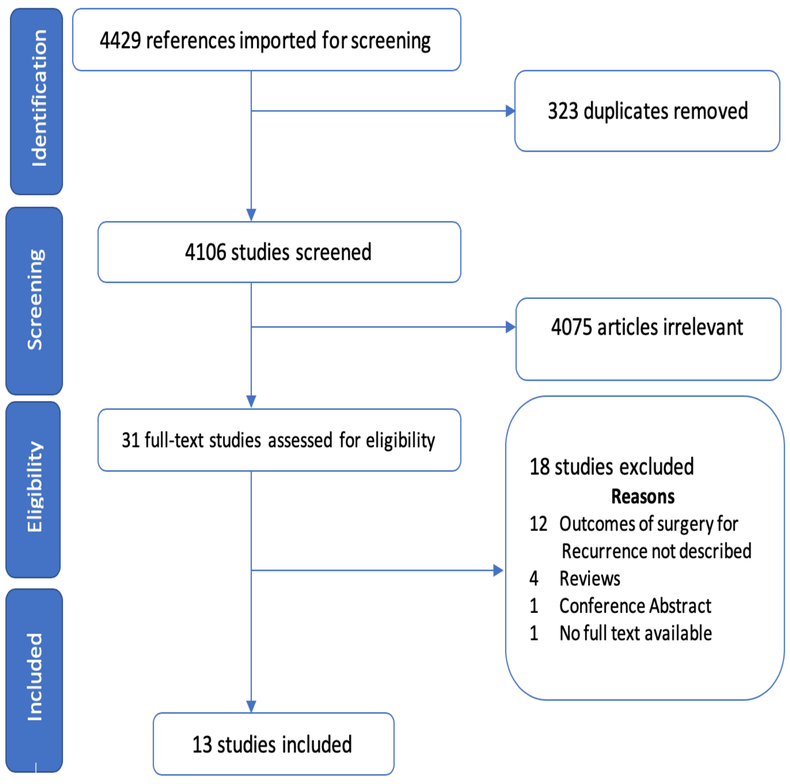

Figure 1. Study Selection process

- Of **4429** references screened, **13** case series, (**605 patients**) were included in this study (**7** studies reported on **RAR**, **5** on **RAS**, while one study reported a stratified analysis on both treatments).
- Pooled incidences were **gross total resection** (GTR) (9 studies; 70%; I^2=82%, 95%CI: 56%, 81%; p-heterogeneity <0.01), **complication** (11 studies; 11%; I^2=48%; 95%CI: 11%, 23%; p-heterogeneity = 0.04), **local failure** (9 studies; 31%, I^2=38%; 95%CI: 19%, 48%; p-heterogeneity = 0.11), and intracranial failure (8 studies; 55%; I^2 = 56%; 95%CI: 48%, 63%; p-heterogeneity = 0.03).
- Stratifying by initial treatment (RAR vs RAS), the pooled incidence comparing RAR to RAS were; **GTR (69% vs 74%), complication (11% vs 16%), local failure (37% vs 28%), intracranial failure (54% vs 56%), six-months survival (83% vs 67)** and **one-year survival (50% vs 36%),** respectively with **P-interaction >0.05**.

Table 1: Study and Patient Characteristics

Author. year	Country of study	Total nr. of patients w/ craniotomy for recurrent BMs	Nr. of patients w/ craniotomy for local recurrence	Men/ women	Mean or median age at diagnosis	Mean or median preoperative KPS
Studies reporting resection after initial resection (n = 8)						
Hulsbergen (post-resection recurrence)	US	63	63	25/38	56	*NR*
Kamp 2018	Germany	36	32	18/18	59	90
Kennion 2017	UK	29	26	14/15	57	75
Schackert 2013	Germany	67	32	33/34	59	*NR*
Al-Zabin 2010	Germany	25	21	19/6	56	80
Arbit 1995	US	32	*NR*	14/18	56	77
Bindal 1995	US	48	32	24/24	48	80
Sundaresan 1988	US	21	14	11/11	52	*NR*
Total or median of medians	-	321	220 (+)	158/163	56	80
Studies reporting resection after initial SRS (n = 6)						
Hulsbergen (post-SRS recurrence)	US	88	88	45/72	60	*NR*
Jeon 2016	Korea	14	14	8/6	56	90
Mu 2015	US	31	31	15/16	55	*NR*
Kano 2009	US	58	58	31/27	54	80
Truong 2006	US	32	32	12/20	53	90
Vecil 2005	US	61	61	37/24	55	80
Total or median or medians	-	284	284	148/136	55	85

Legend: All studies were retrospective observational studies. BM = Brain Metastasis. KPS = Karnofsky Performance Scale. NR = Not Reported. SRS = Stereotactic Radiosurgery. UK = United Kingdom. US = United States. WBRT = Whole-Brain Radiotherapy.

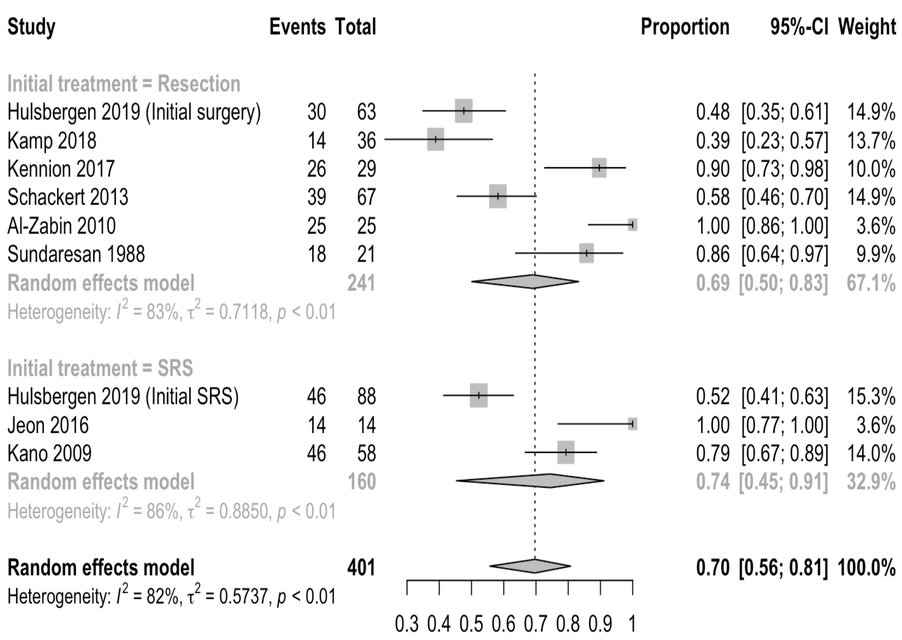

Figure 2. Extent of Resection

Forest plot represents the extent of resection for RAR and RAS among patients with recurrent BMs. Horizontal lines denote 95% CIs; solid squares represent the point estimate of each study and the diamond represents the pooled estimate of the GTR. The size of the solid squares is proportional to the weight of the study. (I^2 for RAR =83.0%; p-heterogeneity<0.01; I^2 for RAS- = 86.0%; p-heterogeneity<0.011 ; overall I^2 = 82.0%; p-heterogeneity<0.01)

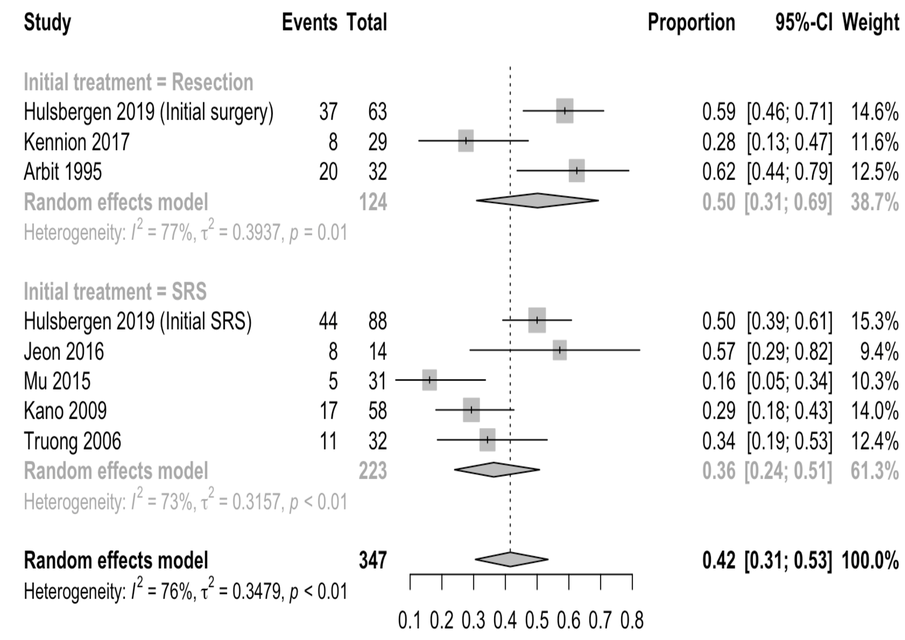

Figure 3. One-year Survival

Forest plot represents six months survival for RAR and RAS among patients with recurrent BMs. Horizontal lines denote 95% CIs; solid squares represent the point estimate of each study and the diamond represents the pooled estimate of the GTR. The size of the solid squares is proportional to the weight of the study. (I^2 for RAR =77.0%; ; I^2 for RAS- = 76.0%; p-heterogeneity=0.03 ; overall I^2 = 76.0%; p-heterogeneity<0.01)

Strengths and Limitations

- Our study represents the first comprehensive meta-analysis and review of oncologic and survival outcomes following surgery for recurrent BMs.
- In addition to reporting of multiple outcomes, we stratified our results according to initial treatment providing specific information about initial management.
- All included studies were retrospective and had small sample sizes.
- Not all outcomes were consistently reported across all studies.

Conclusions

- Resection of recurrent BMs following initial resection or radiosurgery was associated with relatively favorable outcomes that were comparable irrespective of initial treatment, offering compelling evidence for consideration of a more aggressive treatment of recurrent BMs.
- Future studies could focus on comparative analyses between craniotomy and other strategies (SRS, WBRT, laser interstitial thermal therapy, chemotherapy, immunotherapy, or best supportive care in recurrent BMs while controlling for potential confounders such as age, performance status and systemic disease.

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