Follow-up and Retreatment of Brain Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Mehta MP, Patel RR. Radiotherapy and radiosurgery for brain metastases. In: Black PM, Loeffler JS, eds. *Cancer of the Nervous System.* 2 ed. Philadelphia: Lippincott, Williams and Wilkins; 2005:657-672.	Review/other-Tx	N/A	Book chapter.	N/A	4
2. Mamon HJ, Yeap BY, Janne PA, et al. High risk of brain metastases in surgically staged IIIA non-small-cell lung cancer patients treated with surgery, chemotherapy, and radiation. *J Clin Oncol.* 2005;23(7):1530-1537.	Observational-Tx	177 consecutive patients	To retrospectively determine the pattern of failure for patients with stage IIIA NSCLC treated with surgery, chemotherapy, and radiation.	Follow up time was 35 months. Median survival was 21 months after surgery with 3 year OS of 34%. Brain was the most common site of failure with 40% of patients developing them at some point. In patients with nonsquamous histology and residual disease after neoadjuvant therapy, the risk of brain metastasis was 53% at 3 years. Patients treated with neoadjuvant therapy for N2-positive stage IIIA NSCLC enjoy an advantage in both OS and PFS if their lymph node status is downstaged to N(0). Because brain metastases constitute the most common site of failure in these patients, future studies focusing on prophylaxis of brain metastases may improve the outcome in patients with stage IIIA NSCLC.	2
3. Chao ST, Barnett GH, Liu SW, et al. Five-year survivors of brain metastases: a single-institution report of 32 patients. *Int J Radiat Oncol Biol Phys.* 2006;66(3):801-809.	Observational-Tx	32 patients	Records of patients diagnosed with brain metastases were reviewed to report patients who survived ≥5 years from brain metastases treated at a single institution. Patients were treated with WBRT, surgery, and/or SRS.	Median survival was 9.3 years for ≥5-year survivors. Female gender correlated with better survival. When these patients were compared with <5-year survivors, age <65 years, control of the primary at diagnosis, no systemic disease, RPA class 1 (P=0.0002 with class 2; P=0.0022 with class 3), and single brain metastasis were associated with long-term survival in the univariate logistic regression model. In the multivariate model, RPA class 1 compared with class 2 (OR=0.39, P=0.0196), surgery (OR=0.16, P<0.0001), and SRS (OR=0.41, P=0.0188) were associated with long-term survival.	2
4. Tan TC, Black PM. Surgery for brain metastases. In: Black PM, Loeffler JS, eds. *Cancer of the Nervous System*. 2 ed. Philadelphia: Lippincott, Williams and Wilkins; 2005:645-656.	Review/other-Tx	N/A	Book chapter.	N/A	4

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5. Karlsson B, Hanssens P, Wolff R, Soderman M, Lindquist C, Beute G. Thirty years' experience with Gamma Knife surgery for metastases to the brain. *J Neurosurg*. 2009;111(3):449-457.	Observational-Tx	1,855 patients	To analyze factors influencing survival time and patterns of distant recurrences after GKS for metastases to the brain.	25 patients survived for longer than 10 years after GKS, and 23 are still alive. Age and primary tumor control were strongly related to survival time. Patients with single metastases had a longer survival than those with multiple metastases, but there was no difference in survival between patients with single and multiple metastases who had controlled primary disease. There were no significant differences in median survival time between patients with 2, 3-4, 5-8, or >8 metastases. The 5-year survival rate was 6% for the whole patient population, and 9% for patients with controlled primary disease. New hematogenous spread was a more significant problem than micrometastases in patients with longer survival.	2

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6. Kondziolka D, Martin JJ, Flickinger JC, et al. Long-term survivors after gamma knife radiosurgery for brain metastases. *Cancer*. 2005;104(12):2784-2791.	Observational-Tx	677 patients	To evaluate all brain metastasis in patients who lived for ≥4 years after radiosurgery to determine clinical and treatment patterns potentially responsible for their outcome.	44 patients (6.5%) survived for >4 years after radiosurgery (mean, 69 months with 16 patients still alive). The mean age at radiosurgery was 53 years (maximum age, 72 years), and the median KPS was 90. The lung (n = 15 patients), breast (n = 9 patients), kidney (n = 7 patients), and skin (melanoma; n = 6 patients) were the most frequent primary sites. 2 or more organ sites outside the brain were involved in 18 patients (41%), the primary tumor plus lymph nodes were involved in 10 patients (23%), only the primary tumor was involved in 9 patients (20%), and only brain disease was involved in 7 patients (16%), indicating that extended survival was possible even in patients with multiorgan disease. Serial imaging of 133 tumors showed that 99 tumors were smaller (74%), 22 tumors were unchanged (17%), and 12 tumors were larger (9%). 4 patients had a permanent neurologic deficit after brain tumor management, and 6 patients underwent a resection after radiosurgery. Compared with the patients who had limited survival (<3 months), long-term survivors had a higher initial KPS (P=0.01), fewer brain metastases (P=0.04), and less extracranial disease (P<0.00005).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
7. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol.* 2011;29(2):134-141.	Experimental-Tx	359 patients	A phase III trial to assess whether adjuvant WBRT increases the duration of functional independence after surgery or radiosurgery of brain metastases.	Of 359 patients, 199 underwent radiosurgery, and 160 underwent surgery. In the radiosurgery group, 100 patients were allocated to observation, and 99 were allocated to WBRT. After surgery, 79 patients were allocated to observation, and 81 were allocated to adjuvant WBRT. The median time to WHO performance status more than 2 was 10.0 months (95% CI, 8.1 to 11.7 months) after observation and 9.5 months (95% CI, 7.8 to 11.9 months) after WBRT (P=.71). OS was similar in the WBRT and observation arms (median, 10.9 v 10.7 months, respectively; P=.89). WBRT reduced the 2-year relapse rate both at initial sites (surgery: 59% to 27%, P<.001; radiosurgery: 31% to 19%, P=.040) and at new sites (surgery: 42% to 23%, P=.008; radiosurgery: 48% to 33%, P=.023). Salvage therapies were used more frequently after observation than after WBRT. Intracranial progression caused death in 78 (44%) of 179 patients in the observation arm and in 50 (28%) of 180 patients in the WBRT arm.	1
8. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA.* 2006;295(21):2483-2491.	Experimental-Tx	132 patients	To determine if WBRT combined with SRS results in improvements in survival, brain tumor control, functional preservation rate, and frequency of neurologic death.	The median survival time and the 1-year actuarial survival rate were 7.5 months and 38.5% (95% CI, 26.7%–50.3%) in the WBRT + SRS group and 8.0 months and 28.4% (95% CI, 17.6%–39.2%) for SRS alone (P=.42). The 12-month brain tumor recurrence rate was 46.8% in the WBRT + SRS group and 76.4% for SRS alone group (P<.001). Salvage brain treatment was less frequently required in the WBRT + SRS group (n = 10) than with SRS alone (n = 29) (P<.001). Death was attributed to neurologic causes in 22.8% of patients in the WBRT + SRS group and in 19.3% of those treated with SRS alone (P=.64). There were no significant differences in systemic and neurologic functional preservation and toxic effects of radiation.	1

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9. Sadikov E, Bezjak A, Yi QL, et al. Value of whole brain re-irradiation for brain metastases--single centre experience. *Clin Oncol (R Coll Radiol).* 2007;19(7):532-538.	Observational-Tx	72 patients	Retrospective study to document reirradiation of patients with progressive or recurrent brain metastatic disease after initial WBRT.	Most common primary sites were lung (51 patients) and breast (17 patients). The most frequent dose used for the initial radiotherapy was 20 Gy/5 fractions (62 patients). The most common doses of reirradiation were 25 Gy/10 fractions (22 patients), 20 Gy/10 fractions (12 patients), 15 Gy/5 fractions (11 patients) and 20 Gy/8 fractions (10 patients). 31% of patients experienced a partial clinical response after reirradiation. Patients who had Eastern Cooperative Oncology Group performance status 0-1 at the time of retreatment lived longer. In responders, the mean duration of response was 5.1 months. The median survival after reirradiation was 4.1 months. Repeat radiotherapy may be a useful treatment in carefully selected patients. Prospective studies warranted.	2
10. Akiba T, Kunieda E, Kogawa A, Komatsu T, Tamai Y, Ohizumi Y. Re-irradiation for metastatic brain tumors with whole-brain radiotherapy. *Jpn J Clin Oncol.* 2012;42(4):264-269.	Observational-Tx	31 patients	To determine whether second WBRT is beneficial for patients previously treated with WBRT.	The median interval between the initial irradiation and reirradiation was 10 months (range: 2-69 months). The median survival time after reirradiation was 4 months (range: 1-21 months). The symptomatic improvement rate after reirradiation was 68%, and the partial and complete tumor response rate was 55%. 52% of the patients developed Grade 1 acute reactions. On MRI, brain atrophy was observed in 36% of these patients after the initial irradiation and 74% after reirradiation. Grade ≥2 encephalopathy or cognitive disturbance was observed in 10 patients (32%) after reirradiation. Based on univariate analysis, significant factors related to survival after reirradiation were the location of the primary cancer (P=0.003) and the KPS at the time of reirradiation (P=0.008). A KPS ≥70 was significant based on multivariate analysis (P=0.050).	2

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11. Chao ST, Barnett GH, Vogelbaum MA, et al. Salvage stereotactic radiosurgery effectively treats recurrences from whole-brain radiation therapy. *Cancer*. 2008;113(8):2198-2204.	Observational-Tx	111 treated with WBRT and SRS as salvage	To determine the effectiveness of salvage SRS after initial WBRT in terms of OS and local and distant failures.	Median survival after salvage SRS was 9.9 months. Patients with initial recurrence <6 months after SRS had shorter survival after SRS. 25% of patients had local failure after SRS with median time of 5.2 months. Local control at 1 year and 2 years were 68% and 58% respectively. Patients who recurred after WBRT and were treated with salvage SRS were found to have good local control and survival after SRS. WBRT provided good initial control, as 45% of these patients failed >6 months after WBRT. Those with a longer time to failure after WBRT had significantly longer survival after SRS.	2
12. Maranzano E, Trippa F, Casale M, et al. Reirradiation of brain metastases with radiosurgery. *Radiother Oncol.* 2012;102(2):192-197.	Observational-Tx	69 patients	To assess the outcome of reirradiation with SRS of brain metastases recurring after WBRT.	At time of this retrospective analysis all patients had died. The 69 patients reirradiated with SRS had 150 metastases. Median interval between prior WBRT and SRS was 11 months and median SRS prescribed dose was 20 Gy. Response was obtained in 91% of lesions with 1-year local control rate of 74+/-4%. Significantly longer duration of response was associated with higher doses (≥23 Gy) and response achieved after SRS (complete and partial response better than stable disease). Cause of death was brain failure only in 36 (52%) patients. Median OS after reirradiation was 10 months. Variables which significantly conditioned survival were KPS and NFS. 4 (6%) patients had asymptomatic radionecrosis that developed prevalently when lesion diameters were larger and cumulative doses exceeded the values recommended by RTOG 90-05 protocol. About three-fourth of the patients had a good KPS and NFS after reirradiation.	2

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13. Kwon KY, Kong DS, Lee JI, Nam DH, Park K, Kim JH. Outcome of repeated radiosurgery for recurrent metastatic brain tumors. *Clin Neurol Neurosurg.* 2007;109(2):132-137.	Observational-Tx	204 treated initially with GKS; 43 with repeat GKS	To determine the local and distant recurrence rates for patients treated with repeat GKS.	GKS given to previously treated site (37%), new site (30%) and both (33%). Median survival from the second radiosurgical intervention was 36 weeks with local control rate at 6 months of 90.7%. Symptomatic radiation necrosis rate of 18.6%.after second GKS vs 1.5% after first radiosurgical procedure. Recurrence is common for patients with metastatic brain tumors after initial SRS. Local control and survival time after salvage treatment are comparable with those after initial SRS. GKS as a salvage treatment may provide additional survival benefit in selected patients.	2
14. Caballero JA, Sneed PK, Lamborn KR, et al. Prognostic factors for survival in patients treated with stereotactic radiosurgery for recurrent brain metastases after prior whole brain radiotherapy. *Int J Radiat Oncol Biol Phys.* 2012;83(1):303-309.	Observational-Tx	310 patients	To evaluate prognostic factors for survival after SRS for new, progressive, or recurrent brain metastases after prior WBRT.	A total of 310 patients were analyzed, including 90 breast, 113 NSCLC, 31 small-cell lung, 42 melanoma, and 34 miscellaneous patients. The median age was 56, KPS 80, number of brain metastases treated 3, and interval from WBRT to SRS 8.1 months; 76% had controlled primary tumor and 60% had extracranial metastases. The median survival was 8.4 months overall and 12.0 vs 7.9 months for single vs multiple brain metastases treated (P=0.001). There was no relationship between number of brain metastases and survival after excluding single brain metastases patients. On multivariate analysis, favorable prognostic factors included age <50, smaller total target volume, and longer interval from WBRT to SRS in breast cancer patients; smaller number of brain metastases, KPS >60, and controlled primary in NSCLC patients; and smaller total target volume in melanoma patients.	2

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15. Kim PK, Ellis TL, Stieber VW, et al. Gamma Knife surgery targeting the resection cavity of brain metastasis that has progressed after whole-brain radiotherapy. *J Neurosurg.* 2006;105 Suppl:75-78.	Observational-Tx	143 patients	To describe the outcome of using GKS to target the resection cavity in patients whose tumors had progressed after WBRT.	79 of these patients had undergone WBRT prior to resection and GKS. The median patient age was 53 years, and the median prescribed dose was 18 Gy (range 8–24 Gy), with resection cavities of relatively larger volume (>15 cm3). The GKS dose was prescribed at the 40% to 95% isodose contour (mode 50%). Local recurrence within 1 cm of the treatment volume occurred in 4 (5.1%) of 79 cases. The median duration of time to local recurrence was 6.1 months (range 2–13 months). The median duration of time to occurrence of distant metastases following GKS of the resection cavity was 10.8 months (range 2–86 months). Carcinomatous meningitis developed in 4 (5.1%) of 79 cases. Symptomatic radionecrosis requiring surgical treatment occurred in 3 (3.8%) of 79 cases. The median duration of survival following GKS of the resection cavity was 69.6 weeks. The median 2- and 5-year survival rates were 20.2% and 6.3%, respectively.	2
16. Choi CY, Chang SD, Gibbs IC, et al. Stereotactic radiosurgery of the postoperative resection cavity for brain metastases: prospective evaluation of target margin on tumor control. *Int J Radiat Oncol Biol Phys.* 2012;84(2):336-342.	Observational-Tx	112 patients	To examine the outcomes of postoperative resection cavity SRS to determine the effect of adding a 2-mm margin around the resection cavity on local failure and toxicity.	The 12-month cumulative incidence rates of local failure and distant brain failure, with death as a competing risk, were 9.5% and 54%, respectively. On univariate analysis, expansion of the cavity with a 2-mm margin was associated with decreased local failure; the 12-month cumulative incidence rates of local failure with and without margin were 3% and 16%, respectively (P=.042). The 12-month toxicity rates with and without margin were 3% and 8%, respectively (P=.27). On multivariate analysis, melanoma histology (P=.038) and number of brain metastases (P=.0097) were associated with higher distant brain failure. The median OS time was 17 months (range, 2-114 months), with a 12-month OS rate of 62%. Overall, WBRT was avoided in 72% of the patients.	1

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17. Minniti G, Esposito V, Clarke E, et al. Multidose stereotactic radiosurgery (9 Gy x 3) of the postoperative resection cavity for treatment of large brain metastases. *Int J Radiat Oncol Biol Phys.* 2013;86(4):623-629.	Observational-Tx	101 patients	To evaluate the clinical outcomes with linear accelerator-based multidose SRS to large postoperative resection cavities in patients with large brain metastases.	With a median follow-up of 16 months (range, 6-44 months), the 1-year and 2-year actuarial survival rates were 69% and 34%, respectively. The 1-year and 2-year local control rates were 93% and 84%, with respective incidences of new distant brain metastases of 50% and 66%. Local control was similar for radiosensitive (NSCLC and breast cancer) and radioresistant (melanoma and renal cell cancer) brain metastases. On multivariate Cox analysis stable extracranial disease, breast cancer histology, and KPS >70 were associated with significant survival benefit. Brain radionecrosis occurred in 9 patients (9%), being symptomatic in 5 patients (5%).	1
18. Vecil GG, Suki D, Maldaun MV, Lang FF, Sawaya R. Resection of brain metastases previously treated with stereotactic radiosurgery. *J Neurosurg.* 2005;102(2):209-215.	Observational-Tx	61 patients	Retrospective study to review institutional experience with resection of brain metastases following SRS.	Overall median survival time was 11.1 months, with 25% of patients surviving 2 or more years. Complications, morbidity, survival, and recurrence rates are consistent with those seen after conventional surgery for recurrent brain metastases.	2

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19. Truong MT, St Clair EG, Donahue BR, et al. Results of surgical resection for progression of brain metastases previously treated by gamma knife radiosurgery. *Neurosurgery.* 2006;59(1):86-97; discussion 86-97.	Observational-Tx	245 total patients; 32 with resection following progression	Retrospective study to determine the outcomes of surgical resection for progressive lesion after prior GKS and explore factors related to survival after resection.	The 6, 12 and 24 month actuarial survival from time of GKS was 97%, 78%, 47% for the resected patients and 65%, 40%, 19% for the non-resected patients ($P<0.0001$). Tumor was found in 90% of resected specimens and necrosis alone in 10%. Crude rate of local failure following resection was 28% with median time to progression of 6.2 months. Overall, MR spectroscopy or perfusion studies predicted tumor in 11 lesions, confirmed pathologically in 9 lesions, and necrosis alone was found in 2. The MR spectroscopy or perfusion studies predicted necrosis alone in 3, whereas pathology revealed viable tumor in 2 and necrosis in 1 lesion. Surgical intervention of progressive brain metastases after GKS in selected patients leads to a meaningful improvement in survival rates. Further studies are necessary to determine the role of MR spectroscopy or perfusion studies in the post-SRS surveillance of brain metastases.	2
20. Kano H, Kondziolka D, Zorro O, Lobato-Polo J, Flickinger JC, Lunsford LD. The results of resection after stereotactic radiosurgery for brain metastases. *J Neurosurg.* 2009;111(4):825-831.	Observational-Tx	58 patients	Retrospective study. To determine prognostic factors that correlate with survival of patients who require resection of metastasis after SRS.	Overall median survival after resection was 7.7 months. Local control was 62% and 43 % at 1 and 2 years, respectively. Univariate analysis showed pre-op RPA, KPS, systemic disease status, and interval from SRS to resection of >3 months were associated with survival. Surgical morbidity and mortality 1.7% and 6.9%, respectively. In patients with symptomatic mass effect after SRS, resection may be warranted. Patients who had delayed local progression after SRS (>3 months) had the best outcomes after resection.	2
21. Schuette W. Treatment of brain metastases from lung cancer: chemotherapy. *Lung Cancer.* 2004;45 Suppl 2:S253-257.	Review/other-Tx	N/A	To review the utility of chemotherapy for the treatment of brain metastases.	A number of clinical trials have established that brain metastases resulting from both small-cell lung cancer and NSCLC are susceptible to systemic chemotherapy. Further randomized phase-III studies are needed.	4

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22. Kopf B, De Giorgi U, Zago S, Carminati O, Rosti G, Marangolo M. Innovative therapy for patients with brain metastases: oral treatments. *J Chemother*. 2004;16 Suppl 5:94-97.	Review/other-Tx	N/A	To review the utility of oral treatments for patients with brain metastases.	Temozolomide, capecitabine and gefitinib are safe and active in the treatment of CNS metastases from melanoma/recurrent gliomas, breast carcinoma and lung cancer, respectively. New, orally administered drugs hold a great potential for patients with CNS metastases.	4
23. Siena S, Crino L, Danova M, et al. Dose-dense temozolomide regimen for the treatment of brain metastases from melanoma, breast cancer, or lung cancer not amenable to surgery or radiosurgery: a multicenter phase II study. *Ann Oncol*. 2010;21(3):655-661.	Observational-Tx	63 patients	To evaluate the efficacy of single-agent therapy with alternating weekly, dose-dense temozolomide in pretreated patients with brain metastases prospectively stratified by primary tumor type.	In the intent-to-treat population (n = 157; 53 melanoma, 51 breast cancer, and 53 NSCLC), 1 patient had complete response, 9 (6%) had partial responses, and 31 (20%) had stable disease in the brain. Median PFS was 56, 58, and 66 days for melanoma, breast cancer, and NSCLC, respectively. Median OS was 100 days for melanoma, 172 days for NSCLC, and not evaluable in the breast cancer group. Thrombocytopenia was the most common adverse event causing dose modification or treatment discontinuation. Grade 4 toxic effects were rare.	1
24. Hotta K, Kiura K, Ueoka H, et al. Effect of gefitinib ('Iressa', ZD1839) on brain metastases in patients with advanced non-small-cell lung cancer. *Lung Cancer*. 2004;46(2):255-261.	Observational-Tx	57 patients	To retrospectively analyze the efficacy and tolerability of gefitinib in patients with advanced NSCLC.	14/57 patients had brain metastases; 6 experienced objective responses and 8 had stable disease in the brain. 7/14 patients with brain metastases experienced objective responses in their extracranial tumors and, objective responses in the brain were observed in 6 (86%) of these patients. Median survival and median duration of response were 9.1 and 7.7 months, respectively. Gefitinib is effective and well tolerated in patients with refractory NSCLC. Further prospective trials needed in elderly patients and patients with brain metastases.	2
25. Sutherland S, Ashley S, Miles D, et al. Treatment of HER2-positive metastatic breast cancer with lapatinib and capecitabine in the lapatinib expanded access programme, including efficacy in brain metastases--the UK experience. *Br J Cancer*. 2010;102(6):995-1002.	Observational-Tx	162 total patients, 34 with CNS metastasis	To determine the efficacy and safety of capecitabine and lapatinib for patients with metastatic Her2-positive breast cancer including those with brain metastasis.	Of the 34 patients with brain metastasis, 94% had received WBRT prior to enrollment on the trial. By RECIST criteria, 21% had objective response, 48% were judged to have clinical benefit. The median time to progression after enrolling on the trial was 22 weeks.	2

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26. Barlesi F, Gervais R, Lena H, et al. Pemetrexed and cisplatin as first-line chemotherapy for advanced non-small-cell lung cancer (NSCLC) with asymptomatic inoperable brain metastases: a multicenter phase II trial (GFPC 07-01). *Ann Oncol.* 2011;22(11):2466-2470.	Experimental-Tx	43 patients	A trial to assess the safety and efficacy of pemetrexed-cisplatin in this population.	43 patients were enrolled. Initial characteristics were mean age 60.4 years; males 29; PS: 0 in 37.2%, 1 in 60.5% and 2 in 22.3% of patients; adenocarcinoma in 36 patients, large cell in 4 patients (nonsquamous, 93%) and squamous carcinoma in 3 patients. Functional classification of neurological status was stage I/II 86.0%, III 2.3% and IV 11.6%. Grade 3-4 hematological toxic effects were neutropenia, 11 patients (febrile neutropenia, 1 patient), and anemia, 6 patients. Nonhematological toxic effects were grade 2 urinary infection, 1 patient; grade 3 pneumonia, 2 patients; and grade 3 hypoacousia, 1 patient. Cerebral, extracerebral and overall RR by intent to treat analysis were 41.9%, 34.9% and 34.9%, respectively. Median survival time and time to progression were 7.4 and 4.0 months, respectively.	4
27. Lee DH, Han JY, Kim HT, et al. Primary chemotherapy for newly diagnosed nonsmall cell lung cancer patients with synchronous brain metastases compared with whole-brain radiotherapy administered first : result of a randomized pilot study. *Cancer.* 2008;113(1):143-149.	Experimental-Tx	48 patients	To investigate whether primary chemotherapy was feasible in terms of efficacy, survival, toxicity profile, and quality of life compared with WBRT given first in chemotherapy-naive patients NSCLC with synchronous brain metastasis when neurologic symptoms or signs are absent or controlled by supportive care.	A total of 48 patients were enrolled between August 2002 and November 2005. The response rate of chemotherapy and survival outcomes in the primary chemotherapy arm were not statistically different from those in the WBRT-first arm (overall response rate, 28.0% vs 39.1%; PFS, 3.6 months vs 4.4 months; OS, 9.1 months vs 9.9 months). There was close correlation noted between intracranial and extracranial tumor responses (k = 0.82). However, in the WBRT-first arm, grade 3 of 4 neutropenia was more frequent (79% vs 40%) during chemotherapy and 4 patients (17.4%) did not receive further chemotherapy because of early death or poor performance after WBRT. Cognitive function appeared to deteriorate during primary chemotherapy, but was also found to deteriorate after WBRT.	1

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28. Nieder C, Norum J, Dalhaug A, Aandahl G, Pawinski A. Radiotherapy versus best supportive care in patients with brain metastases and adverse prognostic factors. *Clin Exp Metastasis.* 2013;30(6):723-729.	Observational-Tx	113 patients	To compare best supportive care to WBRT in patients with different primary tumors and poor prognosis where uncertainty about the benefit of WBRT exists.	Median OS of all 113 patients was 2 months. No significant difference between best supportive care and 20 Gy WBRT was observed. A slight but significant improvement was observed in the 30 Gy WBRT group (median 2.2 vs 1.7 months). The magnitude of difference is not clinically meaningful. Subgroup analyses revealed that improved survival after 30 Gy WBRT was limited to patients with primary small cell lung cancer.	2
29. Langley RE, Stephens RJ, Nankivell M, et al. Interim data from the Medical Research Council QUARTZ Trial: does whole brain radiotherapy affect the survival and quality of life of patients with brain metastases from non-small cell lung cancer? *Clin Oncol (R Coll Radiol).* 2013;25(3):e23-30.	Experimental-Tx	151 patients	A phase III trial comparing optimal supportive care + WBRT versus optimal supportive care in patients with inoperable brain metastases from NSCLC.	Between March 2007 and April 2010, 151 (of the planned 534) patients were randomized (75 optimal supportive care + WBRT, 76 optimal supportive care). Participants' baseline demographics included median age 67 years (interquartile range 62–73), 60% male, 50% with a KPS <70; steroid usage was similar in the 2 groups; 64/75 (85%) received WBRT (20 Gy/5 fractions). Median survival was: optimal supportive care + WBRT 49 days (95% CI, 39–61), optimal supportive care 51 days (95% CI, 27–57), and hazard ratio 1.11 (95% CI, 0.80–1.53) in favor of WBRT. Quality of life assessed using EQ-5D showed no evidence of a difference. The estimated mean quality-adjusted life years was: optimal supportive care + WBRT 31 days and optimal supportive care 30 days, difference -1 day (95% CI, -12.0 to +13.2 days).	1
30. Sheehan JP, Yen CP, Nguyen J, Rainey JA, Dassoulas K, Schlesinger DJ. Timing and risk factors for new brain metastasis formation in patients initially treated only with Gamma Knife surgery. Clinical article. *J Neurosurg.* 2011;114(3):763-768.	Observational-Tx	117 patients	To better understand timing of new brain metastasis, determine most appropriate treatments and follow-up for patients with brain metastasis after GKS.	Median time to develop new metastasis was 8.8 months. Patients with 3 or more metastasis at time of initial GKS or who had histologies other than NSCLC were more likely to have additional CNS metastasis. 3-month imaging interval appears appropriate for high risk patients.	2

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31. Wang SX, Boethius J, Ericson K. FDG-PET on irradiated brain tumor: ten years' summary. *Acta Radiol*. 2006;47(1):85-90.	Observational-Dx	117 consecutive patients	To evaluate FDG-PET in post-radiotherapy differentiation of tumor recurrence/malignant degeneration and radiation reaction and to assess the role of PET in terms of survival.	61 true-positive, 2 false-positive, 15 false-negative, and 51 true-negative PET examinations; 5 positive and 22 negative PET examinations were indeterminate. PPV of PET was 96% in all and 100% in brain metastases from lung carcinoma. NPV based on the histopathologic results was 55.6%. Survival time was significantly longer in patients with negative PET.	3
32. Terakawa Y, Tsuyuguchi N, Iwai Y, et al. Diagnostic accuracy of 11C-methionine PET for differentiation of recurrent brain tumors from radiation necrosis after radiotherapy. *J Nucl Med*. 2008;49(5):694-699.	Observational-Dx	77 patients	To evaluate the diagnostic accuracy of PET with 11C-methionine for the differentiation of recurrent brain tumors from radiation necrosis.	The values of each index of 11C-methionine PET tended to be higher for tumor recurrence than for radiation necrosis. There were significant differences between tumor recurrence and radiation necrosis in all of the indices except for the L/N(max) for glioma. Receiver operator characteristic analysis indicated that the L/N(mean) was the most informative index for differentiating between tumor recurrence and radiation necrosis. An L/N(mean) of >1.41 provided the best sensitivity and specificity for metastatic brain tumor (79% and 75%, respectively), and an L/N(mean) of >1.58 provided the best sensitivity and specificity for glioma (75% and 75%, respectively).	2
33. Vidiri A, Guerrisi A, Pinzi V, et al. Perfusion Computed Tomography (PCT) adopting different perfusion metrics: recurrence of brain metastasis or radiation necrosis? *Eur J Radiol*. 2012;81(6):1246-1252.	Observational-Dx	12 patients	To determine the accuracy of perfusion CT in differentiating recurrence of brain metastases from radiation necrosis in patients who previously underwent stereotactic radiation therapy.	The differences between the patient's group with recurrence and that with radiation necrosis resulted statistically significant for all the metrics, showing the lowest p-value for V(1.75) and V(2). The metrics based on the fractional volumes were found to show higher predictive powers, with the highest value of 0.96 for V(2.0). Quantitative analysis of the CBV map deriving different metrics may potentially improve the diagnostic accuracy of perfusion CT in differentiating brain metastasis recurrence from radiation necrosis.	3

Follow-up and Retreatment of Brain Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
34. Kano H, Kondziolka D, Lobato-Polo J, Zorro O, Flickinger JC, Lunsford LD. T1/T2 matching to differentiate tumor growth from radiation effects after stereotactic radiosurgery. *Neurosurgery*. 2010;66(3):486-491; discussion 491-482.	Observational-Tx	58 patients	To evaluate prognostic factors that correlate with the survival of patients who require a resection of a brain metastasis after SRS.	At a median follow-up of 7.6 months, 8 patients (14%) were living and 50 patients (86%) had died. The survival after surgical removal was 65%, 30%, and 16% at 6, 12, and 24 months, respectively (median survival after resection 7.7 months). The local tumor control rate after resection was 71%, 62%, and 43% at 6, 12, and 24 months, respectively. A univariate analysis revealed that patient preoperative RPA classification, KPS status, systemic disease status, and the interval between SRS and resection were factors associated with patient survival. The mortality and morbidity rates of resection were 1.7% and 6.9%, respectively.	2
35. Hoefnagels FW, Lagerwaard FJ, Sanchez E, et al. Radiological progression of cerebral metastases after radiosurgery: assessment of perfusion MRI for differentiating between necrosis and recurrence. *J Neurol.* 2009;256(6):878-887.	Observational-Dx	31 patients with 34 lesions	To determine the capability of perfusion MRI for differentiating between radiation induced tumor necrosis and tumor progression in patients treated with SRS.	Tumor recurrence was diagnosed in 20 lesions with necrosis in the remaining 14. The visual inspection of the relative CBV map yielded sensitivity and specificity of 70% and 90% for diagnosis recurrent disease. In patients with a relative CBV-gray matter >1.85, the diagnosis of necrosis was excluded. Salvage treatment can be initiated for these patients in an attempt to prolong survival.	3
36. Mitsuya K, Nakasu Y, Horiguchi S, et al. Perfusion weighted magnetic resonance imaging to distinguish the recurrence of metastatic brain tumors from radiation necrosis after stereotactic radiosurgery. *J Neurooncol.* 2010;99(1):81-88.	Observational-Dx	27 patients	Prospective study to determine if the CBV measured by perfusion MR can predict recurrences vs necrosis. Patients were imaged with perfusion MR and followed if found to have enlarging lesion after SRS.	21 of the 28 lesions were determined to be necrosis while the remaining 7 were recurrences. The relative CBV ratio in the region of interest >2.1 had sensitivity and specificity of 100% and 95.2% respectively for identifying recurrent metastatic disease.	3
37. Barajas RF, Chang JS, Sneed PK, Segal MR, McDermott MW, Cha S. Distinguishing recurrent intra-axial metastatic tumor from radiation necrosis following gamma knife radiosurgery using dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging. *AJNR Am J Neuroradiol.* 2009;30(2):367-372.	Observational-Dx	27 patients	To determine whether relative CBV, relative peak height, and percentage of signal-intensity recovery derived from dynamic susceptibility-weighted contrast-enhanced perfusion MRI can distinguish recurrent metastatic tumor from radiation necrosis.	The mean, minimum, and maximum percentage of signal-intensity recovery values were significantly lower ($P<.01$) in cases of recurrent metastatic tumor. The mean and maximum relative CBV and relative peak height values were significantly higher ($P<.02$) in the recurrent metastatic tumor group.	3

Follow-up and Retreatment of Brain Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
38. Yamamoto M, Kawabe T, Higuchi Y, et al. Delayed complications in patients surviving at least 3 years after stereotactic radiosurgery for brain metastases. *Int J Radiat Oncol Biol Phys.* 2013;85(1):53-60.	Review/other-Tx	167 patients	To assess the incidence and predictors of delayed complications.	Among the 167 patients, 17 (10.2%, 18 lesions) experienced delayed complications (mass lesions with or without cyst in 8, cyst alone in 8, edema in 2) occurring 24.0-121.0 months (median, 57.5 months) after GKS. The actuarial incidences of delayed complications estimated by competing risk analysis were 4.2% and 21.2% at the 60th month and 120th month, respectively, after GKS. Among various pre-GKS clinical factors, univariate analysis demonstrated tumor volume-related factors: largest tumor volume (hazard ratio, 1.091; 95% CI, 1.018–1.154; *P*=.0174) and tumor volume ≤10 cc vs >10 cc (hazard ratio, 4.343; 95% CI, 1.444–12.14; *P*=.0108) to be the only significant predictors of delayed complications. Univariate analysis revealed no correlations between delayed complications and radiosurgical parameters (ie, radiosurgical doses, conformity and gradient indexes, and brain volumes receiving >5 Gy and >12 Gy). After GKS, an area of prolonged enhancement at the irradiated lesion was shown to be a possible risk factor for the development of delayed complications (hazard ratio, 8.751; 95% CI, 1.785–157.9; *P*=.0037). Neurosurgical interventions were performed in 13 patients (14 lesions) and mass removal for 6 lesions and Ommaya reservoir placement for the other 8. The results were favorable.	4

Evidence Table Key

Study Quality Category Definitions

- *Category 1* The study is well-designed and accounts for common biases.
- *Category 2* The study is moderately well-designed and accounts for most common biases.
- *Category 3* There are important study design limitations.
- *Category 4* The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:

  a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
  b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
  c) the study is an expert opinion or consensus document.

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

CBV = Cerebral blood volume

CI = Confidence interval

CNS = Central nervous system

FDG-PET = Fluorine-18-2-fluoro-2-deoxy-D-glucose-positron emission tomography

GKS = Gamma knife radiosurgery

KPS = Karnofsky Performance Status

MRI = Magnetic resonance imaging

NPV = Negative predictive value

NSCLC = Non-small-cell lung cancer

OR = Odds ratio

OS = Overall survival

PFS = Progression-free survival

PPV = Positive predictive value

RPA = Recursive partitioning analysis

RR = Relative risk

SRS = Stereotactic radiosurgery

WBRT = Whole-brain radiation therapy