Single Brain Metastasis
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
1. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys* 1997; 37(4):745-751.	3a	1,200 total patients from 3 consecutive trials	Retrospective review. RPA of prognostic factors from three consecutive phase III brain metastases studies.	According to RPA tree: Best survival (median: 7.1 months) was seen in patients <65 years of age with a KPS of at least 70, and a controlled primary tumor with the brain the only site of metastases. Worst survival (median: 2.3 months) was seen in patients with a KPS <70. Study suggests the following: Class 1: patients with KPS ≥70, <65 years of age with controlled primary and no extracranial metastases; Class 3: KPS <70; Class 2- all others.	2
2. Sperduto PW, Berkey B, Gaspar LE, Mehta M, Curran W. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. *Int J Radiat Oncol Biol Phys* 2008; 70(2):510-514.	15	1,960 patients from database from 5 randomized trials	To introduce a new prognostic index for patients with brain metastases using five consecutive phase III Radiation Therapy Oncology Group (RTOG) brain metastases trials.	RPA and the new GPA had the most statistically significant differences between classes (P<0.001 for all classes). Study concludes that new index, the GPA, is as prognostic as the RPA and more prognostic than the other indices. The GPA is the least subjective, most quantitative and easiest to use of the four indices. Future clinical trials needed.	1
3. Sperduto PW, Kased N, Roberge D, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol* 2012; 30(4):419-425.	15	3,940 patients	To present the updated diagnosis-specific GPA indices in a single, unified, user-friendly report to allow ease of access and use by treating physicians.	Significant prognostic factors varied by diagnosis. For lung cancer, prognostic factors were KPS, age, presence of extracranial metastases, and number of brain metastases, confirming the original Lung-GPA. For melanoma and renal cell cancer, prognostic factors were KPS and the number of brain metastases. For breast cancer, prognostic factors were tumor subtype, KPS, and age. For gastrointestinal cancer, the only prognostic factor was the KPS. The median survival times by GPA score and diagnosis were determined.	2
4. Noordijk EM, Vecht CJ, Haaxma-Reiche H, et al. The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. *Int J Radiat Oncol Biol Phys* 1994; 29(4):711-717.	1	66 patients (63 evaluable)	Randomized trial to determine if surgical resection added to external beam leads to increase in survival or better quality-of-life in patients with single metastasis.	Patients with good performance status, young age, controlled or absence of extracranial disease benefits from the addition of surgical resection with external beam WBRT. Those with uncontrolled extracranial disease or multiple intracranial metastases should receive external beam alone.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
5. 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; 322(8):494-500.	1	48 total patients; 25 in the surgical group and 23 in the radiation group	To look at benefit of surgery and RT vs RT alone for patients with solitary brain metastases. Biopsy confirmation of pathology required in all patients.	11% of patients with solitary brain lesion and known systemic cancer had something other than metastasis on biopsy. Recommended stereotactic biopsy or resection to confirm diagnosis of suspected solitary brain metastasis.	1
6. Mintz AH, Kestle J, Rathbone MP, et al. A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. *Cancer* 1996; 78(7):1470-1476.	1	43 patients RT alone; 41 patients surgery plus RT	Randomized trial to assess efficacy of surgery plus radiation compared with radiation alone in patients with a single cerebral metastasis.	Failure to demonstrate the benefit of the addition of surgical resection to survival or quality-of-life improvement. Further clinical trials needed.	2
7. Borgelt B, Gelber R, Larson M, Hendrickson F, Griffin T, Roth R. Ultra-rapid high dose irradiation schedules for the palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 1981; 7(12):1633-1638.	1	138 – first study; 64 – second study	Randomized phase III trials to study the effectiveness of different time dose RT schemes on the palliation of patients with brain metastases'.	No survival difference for various dose/fractionation regimens. Duration of improvement, rate of disappearance of neurologic symptoms, and time to progression of neurological status worse with very short regimens completed in 1-2 days. The results of the first and second RTOG studies suggest that ultra-rapid, high dose irradiation schedules may not be as effective as higher dose schedules in the palliation of patients with brain metastases. The administration of ultra-rapid schedules should be limited to patients who are unlikely to tolerate more protracted RT regimens.	1
8. Chatani M, Matayoshi Y, Masaki N, Inoue T. Radiation therapy for brain metastases from lung carcinoma. Prospective randomized trial according to the level of lactate dehydrogenase. *Strahlenther Onkol* 1994; 170(3):155-161.	1	162 patients	Prospective randomized trial to determine the best treatment schedule for RT on brain metastasis from lung carcinoma. Study (1985-1992) examined two sequential trials stratified by the level of LDH.	A short course (30 Gy/10 fractions/2-weeks) is an advantageous RT because of the short treatment time for normal LDH and neurological improvement and minor toxicity for the high LDH group, while an optional treatment may be necessary for the selected patients.	1
9. Chatani M, Teshima T, Hata K, Inoue T. Prognostic factors in patients with brain metastases from lung carcinoma. *Strahlenther Onkol* 1986; 162(3):157-161.	1	70 consecutive patients	Two randomized trials to examine the effectiveness of different time-dose RT schemes (30 Gy/10 fractions/2-weeks vs 50 Gy/20 fractions/4-weeks) and the prognostic factors on the palliation for patients with brain metastases from lung carcinoma.	The most important factors for predicting poor prognosis were LDH and general performance status. In normal LDH group, the most important factors for predicting poor prognosis were multiplicity of brain metastases, treatment methods and age.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
10. Haie-Meder C, Pellae-Cosset B, Laplanche A, et al. Results of a randomized clinical trial comparing two radiation schedules in the palliative treatment of brain metastases. *Radiother Oncol* 1993; 26(2):111-116.	1	216 total patients	To compare two schedules of brain irradiation: one course of 18 Gy/3 fractions/3 days vs the same fractionation followed by a second course of RT with a 1-month time interval in a randomized trial.	The second course was identical to the first one or delivered 25 Gy/10 fractions/14 days. No difference in OS, nor in the neurologic response or in the incidence of complications was demonstrated. Two clinical factors appeared to be prognostic of the OS: the presence of multiple brain metastases and the presence of extracerebral metastases.	1
11. Harwood AR, Simson WJ. Radiation therapy of cerebral metastases: a randomized prospective clinical trial. *Int J Radiat Oncol Biol Phys* 1977; 2(11-12):1091-1094.	1	101 patients	Randomized study to compare the effectiveness of a single high-dose treatment to that of a fractionated regimen (3000 cGy/10 fractions vs 1000 cGy/1 fractions).	Single dose of 1000 cGy provided as good palliation as fractionated schedules. High percentage (27%) of patients developed acute complications suggesting need to start steroids prior to RT.	1
12. Kurtz JM, Gelber R, Brady LW, Carella RJ, Cooper JS. The palliation of brain metastases in a favorable patient population: a randomized clinical trial by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 1981; 7(7):891-895.	1	255 patients from 31institutions	Randomized study to investigate 3000 cGy/10 fractions vs 5000 cGy/20 fractions in patients with controlled primary and no other systemic metastases.	No significant difference in median survivals. Thus, a higher dose of radiation cannot be said to improve survival for these patients. Neurologic Function class 2 patients had increased likelihood of improvement with 5000 cGy/ 20 fractions. The treatment of choice for the great majority of patients with metastatic cancer to the brain remains a short one of 2-week course of 2000-3000 cGy. The subpopulation of patients who might benefit from more aggressive therapy remains to be defined.	1
13. Murray KJ, Scott C, Greenberg HM, et al. A randomized phase III study of accelerated hyperfractionation versus standard in patients with unresected brain metastases: a report of the Radiation Therapy Oncology Group (RTOG) 9104. *Int J Radiat Oncol Biol Phys* 1997; 39(3):571-574.	1	429 patients	Randomized phase III study to compare 1-year survival and acute toxicity rates between an accelerated hyperfractionated RT (1.6 Gy BID) to a total dose of 54.4 Gy vs an accelerated fractionation of 30 Gy in 10 daily fractions in patients with unresected brain metastasis.	Median survival time was 4.5 months in both arms, no difference in survival in patients with RPA class I characteristics (KPS >70, controlled primary, age <65, no extracranial disease). Study could not demonstrate any improvement in survival when compared to a conventional regimen of 30 Gy in 10 fractions. Accelerated hyperfractionated regimen to 54.4 Gy is not recommended.	1
14. Auchter RM, Lamond JP, Alexander E, et al. A multiinstitutional outcome and prognostic factor analysis of radiosurgery for resectable single brain metastasis. *Int J Radiat Oncol Biol Phys* 1996; 35(1):27-35.	3a	122 patients	Multicenter, retrospective study to evaluate prognostic factors of patients with single brain metastasis who have undergone radiosurgery in conjunction with WBRT.	Functional survival can be obtained in patients who receive radiosurgery and external beam WBRT in individuals with good performance status and without extracranial metastasis.	2

Single Brain Metastasis
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
15. Bindal AK, Bindal RK, Hess KR, et al. Surgery versus radiosurgery in the treatment of brain metastasis. *J Neurosurg* 1996; 84(5):748-754.	3a/3c	93 total patients; 13 patients treated by radiosurgery; 62 patients treated by surgery who were retrospectively matched	Retrospective review to evaluate patients with solitary or multiple brain metastases that underwent SRS or surgery.	The median survival was 7.5 months for patients treated by radiosurgery and 16.4 months for those treated by surgery. Log-rank analysis showed that the higher mortality rate found in the radiosurgery group was due to a greater progression rate of the radiosurgically treated lesions (P=0.0001) and not due to the development of new brain metastasis (P=0.75). Surgery is superior to radiosurgery in the treatment of brain metastasis. Patients who undergo surgical treatment survive longer and have a better local control. The indications for radiosurgery should be limited to surgically inaccessible metastatic tumors or patients in poor medical condition. Surgery should remain the treatment of choice whenever possible.	2
16. O'Neill BP, Iturria NJ, Link MJ, Pollock BE, Ballman KV, O'Fallon JR. A comparison of surgical resection and stereotactic radiosurgery in the treatment of solitary brain metastases. *Int J Radiat Oncol Biol Phys* 2003; 55(5):1169-1176.	3c	97 patients	Retrospective review of solitary brain metastases patients to determine whether neurosurgery or SRS provided better local tumor control and enhanced patient survival.	No significant difference in patient survival (P=0.15); the 1-year survival rate was 56% for the SRS patients and 62% for the neurosurgery patients. Multivariate Cox regression analysis showed a significant prognostic factor for survival was a performance score of 0 or 1. There was a significant (P=0.020) difference in local tumor control between neurosurgery and SRS for solitary brain metastasis; none of the SRS group had local recurrence compared to 19 (58%) of the neurosurgery group.	3
17. Rades D, Kueter JD, Veninga T, Gliemroth J, Schild SE. Whole brain radiotherapy plus stereotactic radiosurgery (WBRT+SRS) versus surgery plus whole brain radiotherapy (OP+WBRT) for 1-3 brain metastases: results of a matched pair analysis. *Eur J Cancer* 2009; 45(3):400-404.	3c	104 patients	To retrospectively evaluate survival, intracerebral control and local control of the treated metastases in 52 patients undergoing WBRT+SRS and in 52 patients undergoing surgery + WBRT.	1-year survival was 56% after WBRT+SRS and 47% after surgery + WBRT. 1-year intracerebral control was 66% and 50%. 1-year local control was 82% and 66%. WBRT+SRS appeared at least as effective as surgery + WBRT regarding treatment outcomes.	3
18. Schoggl A, Kitz K, Reddy M, et al. Defining the role of stereotactic radiosurgery versus microsurgery in the treatment of single brain metastases. *Acta Neurochir (Wien)* 2000; 142(6):621-626.	3c	133 patients	Retrospective, case-control study to compare roles of SRS with microsurgery in the treatment of single brain metastases.	SRS and microsurgery combined with WBRT are comparable modalities. For morbidity and local tumor control, in particular in cases of "radioresistant" primary tumors, SRS is superior. Authors recommend SRS except for cases of large tumors (>3 cm in maximum diameter) and for those with mass effect.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
19. 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.	1	359 patients	The article reports the results of a randomized phase III trial of the European Organization for Research and Treatment of Cancer (EORTC; 22952-26001) that investigated the role of adjuvant WBRT after either surgery or radiosurgery of a limited number of brain metastases from solid tumors, focusing on patients in good condition with stable systemic cancer. It was hypothesized that these patients would have the greatest benefit from the expected increase in intracranial tumor control after WBRT and would thus keep their functional independence for a longer time period.	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
20. Bernstein M, Cabantog A, Laperriere N, Leung P, Thomason C. Brachytherapy for recurrent single brain metastasis. *Can J Neurol Sci* 1995; 22(1):13-16.	3a	10 patients	To evaluate the use of brachytherapy in a small selected group of patients with control of primary disease, who failed in a single cerebral site after previously receiving tumor resection and external beam irradiation for brain metastasis.	Beneficial response with good local control for reasonable time following implant. Larger, randomized studies needed.	4
21. Ostertag CB, Kreth FW. Interstitial iodine-125 radiosurgery for cerebral metastases. *Br J Neurosurg* 1995; 9(5):593-603.	4	93 patients	To evaluate the efficacy of interstitial iodine-125 for solitary brain metastases. Study retrospectively examined the treatment results of three therapeutic regimens: Group A (38 patients), Group B (34 patients), Group C (21 patients).	The use of interstitial implant to the brain is a safe method for the treatment of selected solitary brain metastases, the addition of WBRT did not significantly contribute to local control or survival.	3
22. Rogers LR, Rock JP, Sills AK, et al. Results of a phase II trial of the GliaSite radiation therapy system for the treatment of newly diagnosed, resected single brain metastases. *J Neurosurg* 2006; 105(3):375-384.	2	62 implanted with GliaSite balloon catheter; 54 received brachytherapy	Prospective, multicenter phase II study to evaluate effectiveness of GliaSite Radiation Therapy System (60 Gy to 1 cm depth) in patients with newly diagnosed single brain metastasis.	Local control was 82%-87%.Both median duration of functional independence and survival were 40 weeks. 13 patients underwent reoperation (9 radiation necrosis, 2 radiation necrosis mixed with tumor).	2

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23. Brown PD, Asher AL, Farace E. Adjuvant whole brain radiotherapy: strong emotions decide but rational studies are needed. *Int J Radiat Oncol Biol Phys* 2008; 70(5):1305-1309.	7	N/A	To examine the effect of adjuvant WBRT on tumor control, OS, and cognitive function.	The role of WBRT is yet to be defined properly. Currently, two Phase III trials are underway, that will determine the effect of adjuvant WBRT on patients' quality of life, neurocognitive function, and survival.	3
24. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA* 1998; 280(17):1485-1489.	1	95	Multicenter, randomized, parallel group trial to determine if postoperative RT resulted in improved neurologic control of disease and increased survival.	Brain recurrence was significantly decreased from 70% in observation arm to 18% in WBRT arm. Recurrence in surgical bed was 46% in observation arm vs 10% in WBRT arm. Neurologic death was decreased from 44% in observation arm vs 14% in WBRT arm.	1
25. 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.	1	132 patients	Prospective, multicenter, randomized trial comparing WBRT+SRS vs SRS alone for patients with limited (defined as 4) brain metastases.	The 12-month brain tumor recurrence rate was 46.8% in the WBRT+SRS group and 76.4% for SRS alone group. Salvage brain treatment was less frequently required in the WBRT+SRS group (n=10) than with SRS alone (n=29). 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
26. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet* 2004; 363(9422):1665-1672.	1	333 total patients (from 55 institutions) 167 assigned WBRT and SRS; 164 were allocated WBRT alone	Randomized, multicenter trial to determine whether SRS provided any therapeutic benefit. One to three newly diagnosed brain metastases were randomly allocated either WBRT or WBRT followed SRS boost.	Patients in the SRS group were more likely to have a stable or improved KPS score at 6 months' follow-up than patients allocated WBRT alone (43% vs 27%, respectively; P=0.03). By multivariate analysis, survival improved in patients with an RPA class 1 or a favorable histological status. WBRT and SRS is recommended for treating patients with a single unresectable brain metastasis and for patients with two or three brain metastases.	1
27. Meyers CA, Smith JA, Bezjak A, et al. Neurocognitive function and progression in patients with brain metastases treated with whole-brain radiation and motexafin gadolinium: results of a randomized phase III trial. *J Clin Oncol* 2004; 22(1):157-165.	1	401 patients	To prospectively evaluate neurocognitive function with a nueropsychometric battery before and after WBRT as part of a phase III trial testing WBRT with or without motexafin gadolinium. Patients were randomly assigned.	91% of patients showed a significant decrease on a least one domain of cognition before treatment. Tumor progression led to further neurocognitive decline compared to effects of WBRT.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
28. Li J, Bentzen SM, Renschler M, Mehta MP. Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function. *J Clin Oncol* 2007; 25(10):1260-1266.	3c	208 patients	Analysis of patients from the WBRT arm of phase III trial PCI-P120-9801 evaluating motexafin gadolinium. Neurocognitive function assessed by tests of memory, executive function, and fine motor coordination, was correlated to MRI-measured brain metastasis volume.	Good responders experienced a significantly improved survival (unidirectional P=.03). For all tests, the median time to neurocognitive function deterioration was longer in good compared with poor responders, with statistical significance seen for Trailmaking B (executive function), and two Pegboard tests (fine motor). In long-term survivors, tumor shrinkage significantly correlated with preservation of executive function and fine motor coordination (r=0.68 to 0.88). WBRT-induced tumor shrinkage correlates with better survival and neurocognitive function preservation. Neurocognitive function is stable or improved in long-term survivors. Tumor progression adversely affects neurocognitive function more than WBRT does, thus making enhancement of radiation response a worthwhile aim in this patient population.	2
29. Li J, Bentzen SM, Renschler M, Mehta MP. Relationship between neurocognitive function and quality of life after whole-brain radiotherapy in patients with brain metastasis. *Int J Radiat Oncol Biol Phys* 2008; 71(1):64-70.	3c	208 total patients	To examine the relationship between neurocognitive function and quality of life in patients with brain metastases after WBRT.	All neurocognitive function tests showed statistically significant correlations with activities of daily living, which became stronger at 4 months. Scores on all 8 neurocognitive function tests deteriorated before activities of daily living decline (net lead time 9-153 days); and scores on 6/8 neurocognitive function tests deteriorated before Functional Assessment of Cancer Therapy-Brain-specific (net lead time 9-82 days).	2
30. Aoyama H, Tago M, Kato N, et al. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. *Int J Radiat Oncol Biol Phys* 2007; 68(5):1388-1395.	1	110 patients	Prospective, multicenter, randomized trial to determine effect of omitting WBRT on neurocognitive function for patients with 1-4 brain metastases treated with SRS.	Mini-Mental State Examination (MMSE) was available for 110/132 in phase III trial. Authors measured improvements of ≥3 points in the MMSE. The average duration of deterioration was 165.5 months in WBRT+SRS arm and 7.6 months in the SRS alone group. Authors concluded that control of brain tumor most important factor for stabilizing neurocognitive function.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Strength of Evidence
31. Chang EL, Wefel JS, Maor MH, et al. A pilot study of neurocognitive function in patients with one to three new brain metastases initially treated with stereotactic radiosurgery alone. *Neurosurgery* 2007; 60(2):277-283; discussion 283-274.	3a	58 patients	Data from a pilot study in which neurocognitive function was prospectively measured for patients with 1-3 newly diagnosed brain metastases treated with initial SRS alone. 15 patients were prospectively treated with initial SRS alone.	67% of patients had impairment on one or more tests of neurocognitive function. Although two-thirds of the brain metastasis patients had impaired neurocognitive function at baseline, the majority of five long-term survivors had stable or improved neurocognitive function performance across executive function, learning/memory, and motor dexterity.	3
32. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol* 2009; 10(11):1037-1044.	1	58 patients	Randomized controlled trial to determine whether the learning and memory functions of patients who undergo SRS plus WBRT are worse than those of patients who undergo SRS alone.	Patients treated with SRS plus WBRT were at a greater risk of a significant decline in learning and memory function by 4 months compared with the group that received SRS alone. Initial treatment with a combination of SRS and close clinical monitoring is recommended as the preferred treatment strategy to better preserve learning and memory in patients with newly diagnosed brain metastases.	1
33. Sun A, Bae K, Gore EM, et al. Phase III trial of prophylactic cranial irradiation compared with observation in patients with locally advanced non-small-cell lung cancer: neurocognitive and quality-of-life analysis. *J Clin Oncol* 2011; 29(3):279-286.	1	340 patients	Multicenter, phase III, prospective randomized study was performed to examine the effects of PCI on neurocognitive function and quality of life.	There were no statistically significant differences at 1 year between the two arms in any component of the EORTC-QLQC30 or QLQBN20 (P>.05), although a trend for greater decline in patient-reported cognitive functioning with PCI was noted. There were no significant differences in MMSE (P=.60) or ADLS (P=.88). However, for Hopkins Verbal Learning Test, there was greater decline in immediate recall (P=.03) and delayed recall (P=.008) in the PCI arm at 1 year.	1

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34. Jensen CA, Chan MD, McCoy TP, et al. Cavity-directed radiosurgery as adjuvant therapy after resection of a brain metastasis. *J Neurosurg* 2011; 114(6):1585-1591.	4	112 resection cavities in 106 patients	To examine the use of high-resolution MRI and cavity-directed radiosurgery for the detection and treatment of further metastases.	Radiosurgery was delivered to the resection cavity alone in 57.5% of patients, whereas 24.5% of patients also received treatment for 1 synchronous metastasis, 11.3% also received treatment for 2 synchronous metastases, and 6.6% also received treatment for 3-10 additional lesions. The median OS was 10.9 months. OS at 1 year was 46.8%. The local tumor control rate at 1 year was 80.3%. The disease control rate in distant regions of the brain at 1 year was 35.4%, with a median time of 6.9 months to distant failure. 39/106 patients eventually received salvage WBRT, and the median time to salvage WBRT was 12.6 months. Kaplan-Meier estimates showed that the rate of requisite WBRT at 1 year was 45.9%. Neurological cause-specific survival at 1 year was 50.1%. Leptomeningeal failure occurred in 8 patients. One patient had treatment failure within the resection tract. 7 patients required reoperation: 2 for resection cavity recurrence, 3 for radiation necrosis, 1 for hydrocephalus, and 1 for a CSF cutaneous fistula. On multivariate analysis, a preoperative tumor diameter >3 cm was predictive of local treatment failure.	2

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35. 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.	4	120 cavities in 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.	2
36. Kondziolka D, Martin JJ, Flickinger JC, et al. Long-term survivors after gamma knife radiosurgery for brain metastases. *Cancer* 2005; 104(12):2784-2791.	3a	677 patients	To retrospectively evaluate all brain metastases patients undergoing SRS from 1988-2000 who lived ≥4 years after radiosurgery.	44 patients (6.5%) survived >4 years after radiosurgery. Compared with patients who lived <3 months, long-term survivors had higher initial KPS, fewer brain metastases and less extracranial disease.	2
37. 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.	15	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.	3

Evidence Table Key

Study Type Key

Numbers 1-7 are for studies of therapies while numbers 8-15 are used to describe studies of diagnostics.

1. Randomized Controlled Trial — Treatment
2. Controlled Trial
3. Observation Study
    a. Cohort
    b. Cross-sectional
    c. Case-control
4. Clinical Series
5. Case reviews
6. Anecdotes
7. Reviews
8. Randomized Controlled Trial — Diagnostic
9. Comparative Assessment
10. Clinical Assessment
11. Quantitative Review
12. Qualitative Review
13. Descriptive Study
14. Case Report
15. Other (Described in text)

Strength of Evidence Key

- Category 1 - The conclusions of the study are valid and strongly supported by study design, analysis and results.
- Category 2 - The conclusions of the study are likely valid, but study design does not permit certainty.
- Category 3 - The conclusions of the study may be valid but the evidence supporting the conclusions is inconclusive or equivocal.
- Category 4 - The conclusions of the study may not be valid because the evidence may not be reliable given the study design or analysis.

Abbreviations Key

CT = Computed tomography

GPA = Graded Prognostic Assessment

KPS = Karnofsky Performance Status

LDH = Lactate dehydrogenase

MRI = Magnetic resonance imaging

OR = Odds ratio

OS = Overall survival

PCI = Prophylactic cranial irradiation

RPA = Recursive partitioning analysis

RT = Radiation therapy

SRS = Stereotactic radiosurgery

WBRT = Whole brain radiation therapy