Pre-Irradiation Evaluation of Brain Metastases
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. 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.	Experimental-Tx	331 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 are recommended for treating patients with a single unresectable brain metastasis and for patients with 2 or 3 brain metastases.	1
2. 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). Overall survival was similar in the WBRT and observation arms (median, 10.9 vs 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

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3. Tsao MN, Rades D, Wirth A, et al. Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): An American Society for Radiation Oncology evidence-based guideline. *Pract Radiat Oncol.* 2012;2(3):210-225.	Review/Other-Tx	N/A	To systematically review the evidence for the radiotherapeutic and surgical management of patients newly diagnosed with intraparenchymal brain metastases.	The choice of management in patients with newly diagnosed single or multiple brain metastases depends on estimated prognosis and the aims of treatment (survival, local treated lesion control, distant brain control, neurocognitive preservation). Single brain metastasis and good prognosis (expected survival 3 months or more): For a single brain metastasis >3 to 4 cm and amenable to safe complete resection, WBRT and surgery (level 1) should be considered. Another alternative is surgery and radiosurgery/radiation boost to the resection cavity (level 3). For single metastasis <3 to 4 cm, radiosurgery alone or WBRT and radiosurgery or WBRT and surgery (all based on level 1 evidence) should be considered. Another alternative is surgery and radiosurgery or radiation boost to the resection cavity (level 3). For single brain metastasis (<3 to 4 cm) that is not resectable or incompletely resected, WBRT and radiosurgery, or radiosurgery alone should be considered (level 1). For nonresectable single brain metastasis (>3 to 4 cm), WBRT should be considered (level 3). Multiple brain metastases and good prognosis (expected survival 3 months or more): For selected patients with multiple brain metastases (all <3 to 4 cm), radiosurgery alone, WBRT and radiosurgery, or WBRT alone should be considered, based on level 1 evidence. Safe resection of a brain metastasis or metastases causing significant mass effect and postoperative WBRT may also be considered (level 3). Patients with poor prognosis (expected survival <3 months): Patients with either single or multiple brain metastases with poor prognosis should be considered for palliative care with or without WBRT (level 3).	4

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4. Akeson P, Larsson EM, Kristoffersen DT, Jonsson E, Holtas S. Brain metastases--comparison of gadodiamide injection-enhanced MR imaging at standard and high dose, contrast-enhanced CT and non-contrast-enhanced MR imaging. *Acta Radiol.* 1995;36(3):300-306.	Observational-Dx	16 patients	To compare the abilities of contrast-enhanced CT, noncontrast-enhanced MRI and contrast-enhanced MRI using standard (0.1 mm/kg) and high (0.3 mm/kg) doses of gadodiamide injection to detect brain metastases.	High dose MRI showed significantly more and smaller metastases than any other examination, and gave a higher diagnostic certainty.	2
5. Kuhn MJ, Hammer GM, Swenson LC, Youssef HT, Gleason TJ. MRI evaluation of "solitary" brain metastases with triple-dose gadoteridol: comparison with contrast-enhanced CT and conventional-dose gadopentetate dimeglumine MRI studies in the same patients. *Comput Med Imaging Graph.* 1994;18(5):391-399.	Review/Other-Dx	4 patients	To compare the sensitivity and safety of high dose gadoteridol (Pro Hance) with routine dose gadopentetate dimeglumine (Magnevist) in the detection of intracranial metastases on MRI when a solitary intracranial lesion was detected on contrast-enhanced cranial CT.	18 total metastases demonstrated on MRI compared to 4 on CT. Only 9/18 of these seen on standard dose contrast MRI.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
6. Nussbaum ES, Djalilian HR, Cho KH, Hall WA. Brain metastases. Histology, multiplicity, surgery, and survival. *Cancer*. 1996;78(8):1781-1788.	Review/Other-Tx	729 patients	To evaluate the disease patterns and survival in patients with metastatic brain tumors with special emphasis on the differences between specific tumor types and the impact of surgical intervention.	Primary tumor histologic type in order of descending frequency included NSCLC, breast carcinoma, SCLC, malignant melanoma, renal cell carcinoma, gastrointestinal carcinoma, uterine/vulvar carcinoma, and unknown primary carcinoma. There were 384 patients (53%) with a single brain metastasis, which was encountered most commonly in patients with prostate carcinoma and least often in patients with SCLC. Multiple metastases were present in 345 patients (47%). The median duration from diagnosis to presentation with a brain metastasis was 12 months, ranging from 3 months for patients with NSCLC to 53 months for patients with breast carcinoma. The median duration from presentation with brain metastases to death was 4 months, ranging from 3 months for patients with SCLC to 13 months for patients with prostate carcinoma. Median survival from presentation with brain metastases to death was 5 months for patients with single lesions and 3 months for patients with multifocal disease (P=0.0001). Median survival for patients with a single lesion was 11 months with surgery and 3 months without surgery (P=0.0001). Surgery did not significantly influence survival in patients with multiple metastases.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
7. Schellinger PD, Meinck HM, Thron A. Diagnostic accuracy of MRI compared to CCT in patients with brain metastases. *J Neurooncol.* 1999;44(3):275-281.	Observational-Dx	66 patients	To investigate, what additional information could be gained by contrast-enhanced MRI in patients with solitary brain metastases according to diagnostic contrast-enhanced CT.	31% of patients with solitary brain metastases by CT criteria had multiple metastases found on subsequent MRI. The 2 main characteristics for brain metastases missed by contrast-enhanced CT were the smaller diameter, which averages 2 cm less than in brain metastases identified with both modalities, and a preferential frontotemporal location. MRI is indeed superior to contrast-enhanced CT in the diagnosis of brain metastases the essential reasons besides detection of smaller lesions being a better soft tissue contrast, significantly stronger enhancement with paramagnetic contrast agents, the lack of bone artifacts, fewer partial volume effects, and direct imaging in 3 different planes. Therefore, MRI is indispensable in the diagnostic workup of patients with brain metastases for choosing the optimum therapeutic approach, especially with regard to the decision whether to operate or to primarily irradiate the patient's metastases.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
8. Nagai A, Shibamoto Y, Mori Y, Hashizume C, Hagiwara M, Kobayashi T. Increases in the number of brain metastases detected at frame-fixed, thin-slice MRI for gamma knife surgery planning. *Neuro Oncol.* 2010;12(11):1187-1192.	Observational-Dx	1,045 patients	To evaluate differences in the numbers of brain metastases between conventional contrast-enhanced MRI (6 ± 1 mm slice thickness) taken before patient referral and contrast-enhanced MRI for gamma knife planning.	Increases in the number of metastases were found in 33.7% of the patients, whereas the number was identical in 62.3%. In 4.0%, the number decreased, indicating overdiagnosis at conventional MRI. These proportions did not differ significantly by the interval before gamma knife. An increase from single to multiple metastases was found in 16.0%. Meningeal dissemination was newly diagnosed in 2.3%. On planning images, the proportions of patients with 1, 2, 3, and 4 or more lesions were 37.6%, 19.3%, 9.3%, and 33.8%, respectively. In cases of colorectal cancer and hepatoma, the proportions of patients with a single metastasis (32/61 [52%] and 5/6 [83%], respectively) were higher than that of patients with other malignancies. In about one-third of the patients, an increased number of metastases were found on the thin-slice images. This should be kept in mind when deciding the treatment strategy for brain metastases.	3
9. Kim SY, Kim JS, Park HS, et al. Screening of brain metastasis with limited magnetic resonance imaging (MRI): clinical implications of using limited brain MRI during initial staging for non-small cell lung cancer patients. *J Korean Med Sci.* 2005;20(1):121-126.	Observational-Dx	314 patients: 183 patients newly diagnosed with NSCLC; 131 patients in control group comprised with NSCLC who underwent limited brain MRI only if they had neurologic symptoms	Prospective study to determine whether using limited brain MRI would be sufficient for early screening for brain metastases in patients with NSCLC. Limited MRI approximately one third the cost of usual diagnostic MRI.	A limited brain MRI detected brain metastases in 20% of newly diagnosed NSCLC patients. There was no significant difference in survival outcome between the groups. Patients who had brain metastases alone had a greater overall survival time (49 weeks) than those who had multiple systemic metastases (27 weeks; P=0.0307). Limited brain MRI appears to be a useful, cost-effective method to screen for brain metastases at the time of initial staging. And it may facilitate timely treatment of patients with NSCLC and improve their survival and quality of life.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
10. Runge VM, Wells JW, Nelson KL, Linville PM. MR imaging detection of cerebral metastases with a single injection of high-dose gadoteridol. *J Magn Reson Imaging.* 1994;4(5):669-673.	Observational-Dx	29 patients	To examine the utility of high-dose (0.3 mm/kg) single-injection gadoteridol administration compared with the standard dose of 0.1 mm/kg for detection of brain metastases.	Increase in number of lesions detected at the higher dose. Changed brain metastases number in 3/15 (20%) of cases. Higher dose increased the subjective impression of "reader confidence."	3
11. Yuh WT, Fisher DJ, Runge VM, et al. Phase III multicenter trial of high-dose gadoteridol in MR evaluation of brain metastases. *AJNR Am J Neuroradiol.* 1994;15(6):1037-1051.	Observational-Dx	67 patients	Phase III trial to assess the efficacy and safety profile of high-dose (cumulative dose 0.3 mm/kg) vs standard dose (0.1 mm/kg) gadolinium in patients with suspected brain metastases.	Blinded and unblinded readers identified 5 and 8 patients, respectively, with solitary lesions on standard-dose examination and multiple lesions on high-dose examination. Gadoteridol can be safely administered up to a cumulative dose of 0.3 mm/kg. High-dose contrast studies provide improved lesion detectability and additional diagnostic information over studies performed in the same patients with a 0.1 mm/kg dose and aid in patient diagnosis and treatment. High-dose gadoteridol study may facilitate the care of patients with suspected central nervous system metastasis.	3
12. Ba-Ssalamah A, Nobauer-Huhmann IM, Pinker K, et al. Effect of contrast dose and field strength in the magnetic resonance detection of brain metastases. *Invest Radiol.* 2003;38(7):415-422.	Observational-Dx	22 patients	To compare the diagnostic efficacy of a standard and cumulative triple dose of MRI contrast agent in the evaluation of brain metastases using a high-field 3.0 T MR unit vs a standard field 1.5 T MR unit.	Improved images were obtained with both higher dose of contrast and higher magnet strength. Administration of gadodiamide contrast agent produces higher contrast between tumor and normal brain on 3.0 T than on 1.5 T, resulting in better detection of brain metastases and leptomeningeal involvement.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
13. Saconn PA, Shaw EG, Chan MD, et al. Use of 3.0-T MRI for stereotactic radiosurgery planning for treatment of brain metastases: a single-institution retrospective review. *Int J Radiat Oncol Biol Phys*. 2010;78(4):1142-1146.	Observational-Dx	254 total patients	To investigate the efficacy of 3.0 T MRI for detecting brain metastases for SRS planning.	With a median interval of 17 days (range, 1-82) between scans, the number of metastases detected using 1.5 T MRI system ranged from 1 to 5 and from 1 to 8 using the 3.0 T MRI system. 22% of patients were found to have a greater number of metastases with the 3.0 T MRI system. The difference in number of metastases detected between the 2 scans for the entire cohort ranged from 0 to 6. Neither histology (P=0.52 by chi-square test) nor time between scans (P=0.62 by linear regression) were significantly associated with the difference in number of metastases between scans. The 3.0 T MRI system appears to be superior to a 1.5 T MRI system for detecting brain metastases, which may have significant implications in determining the appropriate treatment modality. Our findings suggest the need for a prospectively designed study to further evaluate the use of a 3.0 T-MRI system for SRS planning in the treatment of brain metastases.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
14. Rowley HA, Scialfa G, Gao PY, et al. Contrast-enhanced MR imaging of brain lesions: a large-scale intraindividual crossover comparison of gadobenate dimeglumine versus gadodiamide. *AJNR Am J Neuroradiol.* 2008;29(9):1684-1691.	Observational-Dx	138 total patients; 113 patients underwent both examinations	To intraindividually compare 0.1-mmol/kg doses of gadobenate dimeglumine with gadodiamide for qualitative and quantitative lesion enhancement.	Final diagnoses were intra-axial tumor, metastasis, extra-axial tumor, or other (47, 27, 18, and 21 subjects, respectively). Readers 1, 2, and 3 demonstrated global preference for gadobenate dimeglumine in 63 (55.8%), 77 (68.1%), and 73 (64.6%) patients, respectively, compared with 3, 2, and 3 patients for gadodiamide (P<.0001, all readers). Highly significant (P<.0001, all readers) preference for gadobenate dimeglumine was demonstrated for all qualitative end points and for contrast-to-noise ratio (increases of 23.3%–34.7% and 42.4%–48.9% [spin-echo and gradient-refocused echo sequences, respectively] for gadobenate dimeglumine compared with gadodiamide). Inter-reader agreement was good for all evaluations (kappa = 0.47–0.69). Significant preference for gadobenate dimeglumine was demonstrated for all lesion subgroup analyses. Significantly greater diagnostic information and lesion enhancement are achieved on brain MRI with 0.1-mmol/kg gadobenate dimeglumine compared with gadodiamide at an equivalent dose.	1
15. Chiang IC, Kuo YT, Lu CY, et al. Distinction between high-grade gliomas and solitary metastases using peritumoral 3-T magnetic resonance spectroscopy, diffusion, and perfusion imagings. *Neuroradiology.* 2004;46(8):619-627.	Observational-Dx	26 patients	Compared the effectiveness of relative cerebral blood volume, apparent diffusion coefficient, and spectroscopic imaging in differentiating between primary high-grade gliomas and solitary metastases.	Conventional MRI characteristics of solitary metastases and primary high-grade gliomas may sometimes be similar, the peritumoral perfusion-weighted and spectroscopic MRI enable distinction between the 2. Diffusion-weighted imaging techniques were complementary techniques to make a differential diagnosis between the 2 malignant tumors.	3
16. Law M, Cha S, Knopp EA, Johnson G, Arnett J, Litt AW. High-grade gliomas and solitary metastases: differentiation by using perfusion and proton spectroscopic MR imaging. *Radiology.* 2002;222(3):715-721.	Observational-Dx	51 patients	To determine whether perfusion-weighted and proton spectroscopic MRI can be used to differentiate high-grade primary gliomas and solitary metastases on the basis of differences in vascularity and metabolite levels in the peritumoral region.	Conventional MRI characteristics of solitary metastases and primary high-grade gliomas may sometimes be similar, perfusion-weighted and spectroscopic MRI enable distinction between the 2.	3

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17. van de Pol M, van Oosterhout AG, Wilmink JT, ten Velde GP, Twijnstra A. MRI in detection of brain metastases at initial staging of small-cell lung cancer. *Neuroradiology.* 1996;38(3):207-210.	Observational-Dx	40 patients	To determine the significance of MRI for staging patients with SCLC.	MRI did not change stage from limited to extensive in patients without neurologic signs or symptoms.	2
18. Ferrigno D, Buccheri G. Cranial computed tomography as a part of the initial staging procedures for patients with non-small-cell lung cancer. *Chest.* 1994;106(4):1025-1029.	Observational-Dx	184 patients	To assess the clinical yield of cranial CT as a part of the initial staging procedure for patients with NSCLC.	10% of patients with an otherwise operable cancer were found to have metastases after brain CT.	3
19. Hooper RG, Tenholder MF, Underwood GH, Beechler CR, Spratling L. Computed tomographic scanning of the brain in initial staging of bronchogenic carcinoma. *Chest.* 1984;85(6):774-776.	Review/Other-Dx	89 patients	To establish the role of CT brain as a screening procedure to exclude metastases in patients with small cell or NSCLC.	No patient with completely normal clinical exam had abnormal CT. 7/16 patients with neurologic signs or symptoms had brain metastases.	4
20. Win T, Laroche CM, Groves AM, Nathan J, Clements L, Screaton NJ. The value of performing head CT in screening for cerebral metastases in patients with potentially resectable non-small cell lung cancer: experience from a UK cardiothoracic centre. *Clin Radiol.* 2004;59(10):935-938.	Review/Other-Dx	105 consecutive patients	Prospective study to evaluate the prevalence of nonsymptomatic brain metastases detected by CT in patients with potentially resectable NSCLC at a single institution over a period of 18 months. A financial analysis was also done.	6 patients were found to have brain metastases. The estimated cost of the unnecessary thoracotomy in these 6 patients was 60% more than the cost of the CT scans in the 105 patients.	4
21. Ludwig V, Komori T, Kolb D, Martin WH, Sandler MP, Delbeke D. Cerebral lesions incidentally detected on 2-deoxy-2-[18F]fluoro-D-glucose positron emission tomography images of patients evaluated for body malignancies. *Mol Imaging Biol.* 2002;4(5):359-362.	Observational-Dx	1,026 consecutive patients	To evaluate the value of including the brain in the field of view of a whole-body FDG-PET study of patients referred for the evaluation of extra-cranial primary malignancies.	FDG-PET screening for cerebral lesions in patients with body malignancy had little clinical impact. Unsuspected cerebral or skull metastases were detected in only 0.4% of the patients.	3
22. Rohren EM, Provenzale JM, Barboriak DP, Coleman RE. Screening for cerebral metastases with FDG PET in patients undergoing whole-body staging of non-central nervous system malignancy. *Radiology.* 2003;226(1):181-187.	Observational-Dx	40 patients	To compare FDG-PET with MRI, to determine the sensitivity and specificity of FDG-PET for detection of cerebral metastases.	Only 61% of brain metastases identified by brain MRI were identified by FDG-PET. Detection of small lesions, (ie, <1.5 cm in diameter), was particularly difficult. FDG-PET had a sensitivity of 75% (12/16) and a specificity of 83% (20/24).	2

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23. Dittmann H, Dohmen BM, Paulsen F, et al. [18F]FLT PET for diagnosis and staging of thoracic tumours. *Eur J Nucl Med Mol Imaging.* 2003;30(10):1407-1412.	Observational-Dx	16 patients	To determine if the nucleoside analogue [18F]fluorothymidine is useful in the staging of patients with thoracic tumors prior to treatment.	[18F]fluorothymidine-PET may be useful in imaging patients with thoracic tumors suspected of having brain metastases due to the low physiological uptake in normal brain. In the liver and the bone marrow, high physiological [18F]fluorothymidine uptake hampers detection of metastases. On the other hand, [18F]fluorothymidine may be favorable for imaging of brain metastases owing to the low physiological uptake.	3
24. Yamane T, Sakamoto S, Senda M. Clinical impact of (11)C-methionine PET on expected management of patients with brain neoplasm. *Eur J Nucl Med Mol Imaging.* 2010;37(4):685-690.	Observational-Dx	89 (11)C-methionine PET scans for 80 patients	To retrospectively examine the clinical efficacy of (11)C-methionine PET in patients with brain neoplasm, especially whether the (11)C-methionine PET changed the clinical management and whether the change was beneficial or detrimental.	Sensitivity, specificity, and accuracy of (11)C-methionine PET was 87.8%, 80.0%, and 85.9%. The intended management was changed in 50.0% of the scans. Detrimental diagnostic impact and beneficial diagnostic impact were observed in 4.3% and 36.2% of the total relevant scans, respectively. (11)C-methionine PET can provide useful information in initial diagnosis and differentiating tumor recurrence from radiation necrosis. Since a few cases did not receive the requisite treatment due to false-negative results of (11)C-methionine PET, management decision should be made carefully, especially in the case of a negative scan.	3
25. Kyritsis AP, Levin VA, Yung WK, Leeds NE. Imaging patterns of multifocal gliomas. *Eur J Radiol.* 1993;16(3):163-170.	Review/Other-Dx	51 consecutive cases: 32 patients were studied with MRI; 13 with CT; 6 with both imaging techniques	To describe the radiologic characteristics and the various patterns of dissemination in 51 patients with multifocal gliomas. Should multifocal lesions be biopsied if no known systemic cancer?	Multiple gliomas could be confused radiologically with metastases.	4

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26. Andersen C, Astrup J, Gyldensted C. Quantitative MR analysis of glucocorticoid effects on peritumoral edema associated with intracranial meningiomas and metastases. *J Comput Assist Tomogr.* 1994;18(4):509-518.	Observational-Tx	23 (13 with metastases)	To quantify change in peritumoral brain edema as a result of dexamethasone.	Peritumoral edema is heterogeneous in terms of the spatial distribution of T1 and, thereby, water content. Glucocorticoids reduce T1 in peritumoral edema around cerebral metastases significantly after a few days of treatment, possibly through a mechanism that reduces edema production below the level of edema resorption. Peritumoral edema surrounding benign meningiomas was not affected by glucocorticoid treatment, contrary to 1 anaplastic meningiomas, which leads to the speculation that malignant tumors may produce substances that are affected by glucocorticoids and are prerequisites for a glucocorticoid effect. Significant reductions in the highest T1 area (super-edema area) were observed after 24 hours of treatment. The anti-edema effect of glucocorticoid may last at least 63 days. A lower dose-dependent threshold for the effect seems to exist.	2
27. Sturdza A, Millar BA, Bana N, et al. The use and toxicity of steroids in the management of patients with brain metastases. *Support Care Cancer.* 2008;16(9):1041-1048.	Review/Other-Tx	88 patients	To document the use of steroids and frequency of their side effects in patients with brain metastases.	90% of physicians responded to the survey. 45% routinely used dexamethasone 4 mg qid (16 mg/day). The others determined the dose of steroid according to the presence or absence of neurological symptoms. 60% tapered the patient's steroids over the 4 weeks following completion of WBRT. The most common side effects noted by physicians were: increased appetite or weight gain (46%), insomnia (24%), gastrointestinal symptoms (20%). In the retrospective study, dexamethasone 4 mg qid was prescribed to 52% patients prior and during WBRT. 66% of patients were instructed to taper dexamethasone after WBRT, but details were not provided. The most frequently documented steroid-related side effects were: increased appetite (32%), proximal muscle weakness (28%), and insomnia (21%).	4

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28. Borgelt B, Gelber R, Kramer S, et al. The palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys.* 1980;6(1):1-9.	Experimental-Tx	26 patients, first study; 33 patients, second study	To present the final results of the 2 optional ultra-rapid, high dose arms of the first 2 RTOG studies.	Comparisons were made with 143 control patients randomized by the same participating institutions to receive a more protracted course of irradiation (2000, 3000 or 4000 rad/l-4 weeks). Responses of patients receiving ultra-rapid treatment, as assessed by the percent who had improvement in neurologic function, was comparable to that of patients receiving the more protracted schedules. Promptness of neurologic function improvement, treatment morbidity and median survival were also comparable to those of patients receiving 2000 to 4000 rad. However, the duration of improvement, time to progression of neurologic status and rate of complete disappearance of neurologic symptoms were generally less for those patients who received 1000 or 1200 rad.	1
29. 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.	Experimental-Tx	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
30. Vecht CJ, Hovestadt A, Verbiest HB, van Vliet JJ, van Putten WL. Dose-effect relationship of dexamethasone on Karnofsky performance in metastatic brain tumors: a randomized study of doses of 4, 8, and 16 mg per day. *Neurology.* 1994;44(4):675-680.	Experimental-Tx	89 patients	To determine whether lower doses of dexamethasone are as effective as conventional dose of 16 mg/d.	Dexamethasone 4 mg/d results in same degree of improvement as 16 mg/d after 1-week of treatment if no signs of impending herniation. Toxic effects occurred more frequently with higher doses.	1
31. Hempen C, Weiss E, Hess CF. Dexamethasone treatment in patients with brain metastases and primary brain tumors: do the benefits outweigh the side-effects? *Support Care Cancer.* 2002;10(4):322-328.	Review/Other-Tx	138 consecutive patients	To retrospectively analyze the advantages and disadvantages of dexamethasone taken during cranial RT.	Side effects were common, and increased with duration of dexamethasone. Life-threatening complications were rare. Dexamethasone effectively minimized neurological symptoms and radiation-related side-effects. Dosage and duration must be decided on individual patient's needs. Future prospective studies will have to determine whether dexamethasone is advantageous on balance or not	4

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32. Papa MZ, Vetto JT, Ettinghausen SE, Mule JJ, Rosenberg SA. Effect of corticosteroid on the antitumor activity of lymphokine-activated killer cells and interleukin 2 in mice. *Cancer Res.* 1986;46(11):5618-5623.	Observational-Tx	48 mice receiving CA; 30 controls	To determine the effect of steroid administration on the toxicity of IL-2 in mice and on the therapeutic effects of immunotherapy with IL-2 or LAK cells plus IL-2 in our murine model.	Cortisone acetate, 25-75 mg/kg, was administered daily to mice receiving high dose IL-2 for 10 days. Cortisone acetate significantly reduced the toxicity induced by IL-2; 38 of 48 mice receiving cortisone acetate survived compared to 0 of 30 controls ($P<0.0001$). In addition, cortisone acetate administration caused a decrease in IL-2-induced 125I-labeled albumin leakage in mouse organs. However, cortisone acetate abrogated the in vivo antitumor effect of high dose IL-2, and to a lesser extent the therapeutic effect of exogenous LAK cells plus lower dose IL-2. Mice treated with 100,000 units of IL-2 showed 98, 63, and 33% reductions of pulmonary metastases in Hanks' balanced salt solution, 25 mg Ca/kg, and 75 mg Ca/kg groups, respectively; treatment with LAK and 7,500 units of IL-2 resulted in reductions of 94, 77, and 57% in these same groups. Cortisone acetate treatment of animals did not affect LAK generation, although the absolute number of LAK precursors was greatly reduced.	1
33. Corsello SM, Salvatori R, Barnabei A, De Vecchis L, Marchetti P, Torino F. Ipilimumab-induced endocrinopathies: when to start corticosteroids (or not). *Cancer Chemother Pharmacol.* 2013;72(2):489-490.	Review/Other-Tx	N/A	Letter.	No results stated.	4
34. Glantz MJ, Cole BF, Forsyth PA, et al. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2000;54(10):1886-1893.	Review/Other-Tx	12 studies	To perform a meta-analysis to determine the efficacy and toxicity of prophylactic anticonvulsant medication.	Prophylactic anticonvulsant medication does not provide substantial reduction of seizure-free survival. Prophylactic anticonvulsant medication was associated with frequent side effects that are occasionally life-threatening.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
35. Forsyth PA, Weaver S, Fulton D, et al. Prophylactic anticonvulsants in patients with brain tumour. *Can J Neurol Sci.* 2003;30(2):106-112.	Experimental-Tx	100 total patients: 46 patients were randomized to the anticonvulsants group; 54 to the no anticonvulsants group	To determine if prophylactic anticonvulsants in brain tumor patients (without prior seizures) reduced seizure frequency.	Prophylactic anticonvulsants did not reduce seizure frequency. Seizure-free survivals at 3 months was 87% and 90% in the anticonvulsant and no anticonvulsant group, respectively (log rank test, P=0.98).	1
36. Glantz MJ, Cole BF, Friedberg MH, et al. A randomized, blinded, placebo-controlled trial of divalproex sodium prophylaxis in adults with newly diagnosed brain tumors. *Neurology.* 1996;46(4):985-991.	Experimental-Tx	74 consecutive patients	Randomized, double-blind, placebo-controlled study to compare the incidence of first seizures in divalproex sodium- and placebo-treated patients with newly diagnosed tumors.	Anticonvulsant prophylaxis not warranted. 35% of patients receiving divalproex sodium and 24% of patients on placebo had seizures.	1
37. Weaver S, DeAngelis LM, Fulton D, et al. A prospective randomized study of prophylactic anticonvulsants in patients with primary or metastatic brain tumors and without seizures. *Ann Neurol.* 1997;42:430.	Observational-Tx	100 patients	Prospective randomized study to determine whether prophylactic anticonvulsants reduce seizure frequency. To determine the toxicity of prophylactic anticonvulsants.	Incidence of seizures (26/100) and seizure-free survival were not significantly different between group assigned to get anticonvulsants and those assigned not to get anticonvulsants. Anticonvulsants toxicities were minor.	1
38. Byrne TN, Cascino TL, Posner JB. Brain metastasis from melanoma. *J Neurooncol.* 1983;1(4):313-317.	Observational-Tx	78 total patients: Group 1, multiple brain metastases treated with RT (n = 49); Group 2, single brain metastasis treated with RT (n = 17); Group 3, single brain metastasis treated with surgery with or without RT (n = 9)	To determine whether prophylactic anticonvulsants reduce seizure frequency in patients with brain metastases from melanoma.	Incidence of seizures in patients receiving or not receiving anticonvulsants was 17% and 37%, respectively. Surgical extirpation should be considered in highly selected patients with brain metastasis from melanoma. Prophylactic anticonvulsants are recommended if there is no contraindication.	2

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

CI = Confidence interval

CT = Computed tomography

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

KPS = Karnofsky Performance Status

MRI = Magnetic resonance imaging

NSCLC = Non-small-cell lung cancer

PET = Positron emission tomography

RPA = Recursive partitioning analysis

RT = Radiation therapy

SCLC = Small-cell lung cancer

SRS = Stereotactic radiosurgery

WBRT = Whole brain radiation therapy