

Bölüm 45

KRANİAL METASTAZLARDA RADYOTERAPİNİN YERİ

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GİRİŞ

Beyin metastazı erişkinlerde en sık görülen intrakranial tümörlerdir. Kanser hastalarının yaklaşık %20-40'ında beyin metastazı gelişebilmektedir (1). Akciğer (%16-20), renal karsinom (%6-10 melanom (%7), meme (%5) ve kolon karsinomu (%1-2) tümörleri en sık beyine metastaz yapan tümörlerdendir (2-3). Beyin metastazlarının prognozu oldukça kötüdür ve nörolojik fonksiyon bozukluğuna bağlı olarak hastaların yaşam kalitelerini de önemli ölçüde etkilemektedir (2). Beyin metastazlı hastalarda, kafa içi basıncının artmasına bağlı semptomlar (baş ağrısı, kusma, güçsüzlük ve nöbetler) olabileceği gibi hemiparezi, afazi, hemianopsi gibi fokal nörolojik defisitler de görülebilmektedir (1). Bu nedenle beyin metastazlarının palyatif tedavisinde bu semptomlara hızla müdahale etmek gerekmektedir. Bu hastalara uygulanacak tedavinin amacı; palyasyon sağlamak ve sinir sistemi fonksiyonlarını koruyabilmektir. Hastanın nörolojik durumu, primer tümörün evresi, metastazların sayısı, büyüklüğü ve yerleşim yeri uygulanacak tedavinin seçiminde dikkate alınması gerekmektedir. Bu sebeple beyin metastazının tedavisinde çeşitli prognostik ölççekler tedavi yöntemine karar verirken kullanılmaktadır.

Son yıllarda cerrahi ve radyocerrahi teknikleri geliştikçe intrakranial hastalığın lokal kontrolü daha iyi sağlamaktadır (4). Beyin metastazlarının tedavisinde cerrahi, stereotaktik radyocerrahi (SRS) ve tüm beyin radyoterapisi (TBRT) yapılmaktadır. TBRT, intrakranial tümör yükü yüksek birçok hasta için birincil tedavi yöntemi olmasına rağmen, SRS veya cerrahi rezeksiyon gibi tedavi yöntemlerinden de faydalanmak gerekmektedir. Çünkü TBRT'si diğer yöntemlere göre daha iyi bir genel sağkallım sağlamamakla birlikte, yan etkiler ve nörokognitif bilişsel bozukluğa bağlı olarak yaşam kalitesini düşürebilmektedir (5-7).

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SRS'nin nörokognitif fonksiyonlar üzerindeki uzun vadeli etkileri iyi çalışılmamıştır, ancak mevcut veriler güven vericidir (57). TBRT'de ise SRS'ye göre daha fazla nörokognitif bozukluklar bildirilmiştir (38).

Nörokognitif bozukluk riskini azaltmak için çeşitli stratejiler aktif olarak araştırılmaktadır (27). Bu araştırmalardan biri memantin ile yapılmıştır. Memantin, beyin metastazlı hastalarda TBRT ile eş zamanlı verilen oral N-metil-D-aspartat (NMDA) reseptör antagonistidir. Çok güçlü kanıtları olmamakla birlikte, bazı çalışmalarda memantinin kognitif bozulma sürecini geciktirebildiği ve hastalar tarafından tolere edilebildiği vurgulanmıştır (58,59). Ancak nörokognitif bozulmayı azaltacak en önemli korunma yolu, radyoterapi sırasında normal dokuların (özellikle hipokampusun) korunması gibi gözükmektedir.

SONUÇ

Sonuç olarak beyin metastazlı hastaların tedavisinde, hastaların performansı, fonksiyonel durumu, hastalığın yaygınlığı, hastalığın pimeri, varsa önceki tedavi modalitesi, metastaz sayısı, tümör hacmi ve rekürrens olup olmadığı göz önüne alınarak SRS, rezeksiyon, TBRT veya bunların kombinasyonları uygulanabilir.

Anahtar kelimeler: Beyin metastazi, radyocerrahi, tüm beyin radyoterapisi.

KAYNAKLAR

1. Usuki KY, Milano MT, David M, Okunieff P, Metastatic disease: bone, spinal cord, brain, liver, and lung. In: Gunderson LL, Tepper JE, editors. Clinical radiation oncology. 4nd ed. Elsevier Saunders; 2016. 443-45.
2. Patchell RA. The management of brain metastases. *Cancer Treat Rev* 2003;29(6):533-40.
3. Kamar FG, Posner JB. Brain metastases. *Semin Neurol* 2010;30:217-35.
4. Barnholtz-Sloan JS, Sloan AE, Davis FG, et al. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J Clin Oncol*. 2004;22(14):2865-72.
5. Gaspar LE, Mehta MP, Patchell RA, et al. The role of whole brain radiation therapy in the management of newly diagnosed brain metastases: A systematic review and evidence-based clinical practice guideline. *J Neurooncol* 2010;96:17-32.
6. Kalkanis SN, Kondziolka D, Gaspar LE, et al. The role of surgical resection in the management of newly diagnosed brain metastases: A systematic review and evidence-based clinical practice guideline. *J Neurooncol* 2010;96:33-43.
7. Nieder C, Nestle U, Walter K, et al. Dose/effect relationships for brain metastases. *J Cancer Res Clin Oncol* 1998;124:346-350.
8. Sperduto PW, Chao ST, Sneed PK, et al. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. *Int J Radiat Oncol Biol Phys* 2010; 77:655.
9. 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;37:745-51.
10. Gerdan L, Segedin B, Nagy V, et al. Brain metastasis from non-small cell lung cancer (NSCLC): prognostic importance of the number of involved extracranial organs. *Strahlenther Onkol* 2014;190(1):64-7.

11. 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; 30:419.
12. Sperduto PW, Deegan BJ, Li J, et al. Estimating survival for renal cell carcinoma patients with brain metastases: an update of the Renal Graded Prognostic Assessment tool. *Neuro Oncol* 2018; 20:1652.
13. Lorenzoni J, Devriendt D, Massager N, et al. Radiosurgery for treatment of brain metastases: estimation of patient eligibility using three stratification systems. *Int J Radiat Oncol Biol Phys* 200;460:218-24.
14. Weltman E, Salvajoli JV, Brandt RA, et al. Radiosurgery for brain metastases: a score index for predicting prognosis. *Int J Radiat Oncol Biol Phys* 2000; 46:1155-61.
15. T sao MN, L loyd N, Wong RKS, et al. Whole brain radiotherapy for the treatment of multiple brain metastases. *Cochrane Database of Syst Rev* 2006;19:3.
16. T sao MN, Lloyd N, Wong RK, et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. *Cochrane Database Syst Rev* 2012;18:4.
17. Rades D, Schild SE, Lohynska R, et al. Two radiation regimens and prognostic factors for brain metastases in nonsmall cell lung cancer patients. *Cancer* 2007;110(5):1077-82.
18. Rades D, Evers JN, Veninga T, et al. Shorter-course whole-brain radiotherapy for brain metastases in elderly patients. *Int J Radiat Oncol Biol Phys* 2011; 81(4):469-73.
19. Noordijk EM, Vecht CJ, Haaxma-Reiche H, et al. The choice of treatment of single brain metastases should be based on extracranial tumor activity and age. *Int J Radiat Oncol Biol Phys* 1994;29:711-17.
20. 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 metastases. *Cancer* 1996;1470-76.
21. 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):1485-89.
22. Gondi V, Pugh SL, Tome WA, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol* 2014;32:3810-6.
23. Oehlke O, Wucherpfennig D, Fels F, et al. Whole brain irradiation with hippocampal sparing and dose escalation on multiple brain metastases: Local tumour control and survival. *Strahlenther Onkol* 2015;191(6):461-9.
24. Shrieve DC, Loeffler JS, McDermott MW, et al. Radiosurgery. In: Hoppe R, Phillips TL, Roach M, eds. *Leibel and Philips textbook of Radiation Oncology*. 3rd ed. Philadelphia PA: Elsevier Saunders, 2010:487-508.
25. Suh JH, Stereotactic radiosurgery for the management of brain metastases. *N Engl J Med* 2010;362:1119-27.
26. 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; 295:2483-91.
27. Change 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;10:1037-44.
28. Muacevic A, Kreth FW, Horstmann GA, et al. Surgery and radiotherapy compared with gamma knife radiosurgery in the treatment of solitary cerebral metastases of small diameter. *J Neurosurg* 1999; 91:35-43.
29. Rades D, Bohlen G, Pluemer A, et al. Stereotactic radiosurgery alone versus resection plus whole-brain radiotherapy for 1 or 2 brain metastases in recursive partitioning analysis class 1 and 2 patients. *Cancer* 2007; 109:2515-21.
30. Muacevic A, Wowra B, Siefert A, et al. Microsurgery plus whole brain irradiation versus Gamma Knife surgery alone for treatment of single metastases to the brain: a randomized controlled multicentre phase III trial. *J Neurooncol* 2008; 87:299-307.

31. Bhatnagar AK, Flickinger JC, Kondziolka D, et al. Stereotactic radiosurgery for four or more intracranial metastases. *Int J Radiat Oncol Biol Phys* 2006; 64:898-903.
32. Shaw E, Scott C, Souhami L, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 9005. *Int J Radiat Oncol Biol Phys* 2000; 47:291.
33. Kocher M, Soffiotti 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; 29:134-41.
34. 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; 363:1665-72.
35. Mahajan A, Ahmed S, McAleer MF, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol* 2017; 18:1040.
36. Mathieu D, Kondziolka D, Flickinger JC, et al. Tumor bed radiosurgery after resection of cerebral metastases. *Neurosurgery* 2008; 62:817.
37. Brennan C, Yang TJ, Hilden P, et al. A phase 2 trial of stereotactic radiosurgery boost after surgical resection for brain metastases. *Int J Radiat Oncol Biol Phys* 2014; 88:130.
38. Brown PD, Ballman KV, Cerhan JH, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC-3): A multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol* 2017; 18:1049.
39. Soltys SG, Adler JR, Lipani JD, et al. Stereotactic radiosurgery of the postoperative resection cavity for brain metastases. *Int J Radiat Oncol Biol Phys* 2008;70:187-93.
40. Brown PD, Ballman KV, Cerhan JH et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC-3): a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol* 2017;18 (8):1049-60.
41. Marks, L.B., Yorke, E.D., Jackson, A. et al. Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys.* 2010;76:10-19.
42. Petrovich Z, Yu C, Giannotta SL, et al. Survival and pattern of failure in brain metastasis treated with stereotactic gamma knife radiosurgery. *J Neurosurg* 2002; 97:499.
43. Sneed PK, Mendez J, Vemer-van den Hoek JG, et al. Adverse radiation effect after stereotactic radiosurgery for brain metastases: incidence, time course, and risk factors. *J Neurosurg* 2015; 123:373.
44. Miller JA, Bennett EE, Xiao R, et al. Association Between Radiation Necrosis and Tumor Biology After Stereotactic Radiosurgery for Brain Metastasis. *Int J Radiat Oncol Biol Phys* 2016; 96:1060.
45. Do L, Pezner R, Radany E, et al. Resection followed by stereotactic radiosurgery to resection cavity for intracranial metastases. *Int J Radiat Oncol Biol Phys* 2009; 73:486.
46. Jensen CA, Chan MD, McCoy TP, et al. Cavity-directed radiosurgery as adjuvant therapy after resection of a brain metastasis. *J Neurosurg* 2011; 114:1585.
47. Brennan C, Yang TJ, Hilden P, et al. A phase 2 trial of stereotactic radiosurgery boost after surgical resection for brain metastases. *Int J Radiat Oncol Biol Phys* 2014; 88:130.
48. Mathieu D, Kondziolka D, Flickinger JC, et al. Tumor bed radiosurgery after resection of cerebral metastases. *Neurosurgery* 2008; 62:817.
49. Minniti G, Scaringi C, Paolini S, et al. Single-Fraction Versus Multifraction (3 × 9 Gy) Stereotactic Radiosurgery for Large (>2 cm) Brain Metastases: A Comparative Analysis of Local Control and Risk of Radiation-Induced Brain Necrosis. *Int J Radiat Oncol Biol Phys* 2016; 95:1142.
50. Lehrer EJ, Peterson JL, Zaorsky NG, et al. Single versus Multifraction Stereotactic Radiosurgery for Large Brain Metastases: An International Meta-analysis of 24 Trials. *Int J Radiat Oncol Biol Phys* 2019; 103:618.
51. Fang P, Jiang W, Allen P, et al. Radiation necrosis with stereotactic radiosurgery combined with CTLA-4 blockade and PD-1 inhibition for treatment of intracranial disease in metastatic

- melanoma. *J Neurooncol* 2017; 133:595.
52. Kim JM, Miller JA, Kotecha R, et al. The risk of radiation necrosis following stereotactic radiosurgery with concurrent systemic therapies. *J Neurooncol* 2017; 133:357.
 53. Martin AM, Cagney DN, Catalano PJ, et al. Immunotherapy and Symptomatic Radiation Necrosis in Patients With Brain Metastases Treated With Stereotactic Radiation. *JAMA* 2018; 4:1123.
 54. Hwang WL, Pike LRG, Royce TJ, et al. Safety of combining radiotherapy with immune-checkpoint inhibition. *Nat Rev Clin Oncol* 2018; 15:477.
 55. Boothe D, Young R, Yamada Y, et al. Bevacizumab as a treatment for radiation necrosis of brain metastases post stereotactic radiosurgery. *Neuro Oncol* 2013;15(9):1257-63
 56. Yamamoto M, Serizawa T, Higuchi Y, et al. A Multi-institutional Prospective Observational Study of Stereotactic Radiosurgery for Patients With Multiple Brain Metastases (JLGK0901 Study Update): Irradiation-related Complications and Long-term Maintenance of Mini-Mental State Examination Scores. *Int J Radiat Oncol Biol Phys* 2017; 99:31.
 57. Day J, Zienius K, Gehring K, et al. Interventions for preventing and ameliorating cognitive deficits in adults treated with cranial irradiation. *Cochrane Database Syst Rev* 2014.
 58. Brown PD, Pugh S, Laack NN, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro Oncol* 2013; 15:1429.