

## Bölüm **42**

# **NÜKS VE PROGRESE SANTRAL SİNİR SİSTEMİ TÜMÖRLERİNDE YENİDEN İŞİNLAMA**

**Birsen YÜCEL<sup>1</sup>**

## **GİRİŞ**

Beyin tümörlerinde primer tedavi cerrahi olmasına rağmen kitlenin tamamını çıkarmak çoğu zaman mümkün değildir. Bu nedenle, düşük yada yüksek grade li glial tümörlerin adjuvan tedavisinde radyoterapinin (RT) yeri bulunmaktadır. Düşük gradeli glial tümörlerde tümör total çıkarıldı ise adjuvan RT'ye genellikle ihtiyaç duyulmaz ancak bunların rekkürrenslerinde RT endikasyonu bulunmaktadır. Düşük gradeli tümörlerde progresyona kadar geçen süre uzundur, fakat bunların çoğunda da relaps gözlenir. Yine, diğer beyin tümörlerinin (medullablastom, menenjiom, germinoma vb.) ilk tedavilerinde RT uygulaması yer almaktadır. Glioblastoma için kitle eksizyonu sonrası standart tedavi, eşzamanlı ve adjuvan temozolomid ile birlikte RT'dir. Bu yaklaşım, cerrahi sonrası tek başına RT ile karşılaşıldığında 5 yıllık genel sağkalımı artmıştır (%1.9 vs. %9.8) (1). Bununla birlikte, sağkalım oranlarındaki artışa rağmen, tümörün infiltratif ve radyorezistant doğasından dolayı rekürrens hala önemli bir problem oluşturmaktadır.

Tekrarlayan gliomaların çoğunda kurtarma tedavisi endikedir ve çoğu hasta relapsta sistemik tedavi ve/veya cerrahi tedavi alır. Yapılan çalışmalarla, re-eksizyonun genişliğinin sağkalım ile ilişkili olduğu gösterilmiştir (2-4). Ancak, cerrahi rezeksiyon uygulaması, sıklıkla bu tümörlerin infiltratif doğası ve ileri cerrahi müdahalelerde ciddi nörolojik defisitlerin ve yüksek mortalite oranlarının oluşması nedeniyle sınırlıdır. Ayrıca bu hastaların performans durumları re-eksizyon için çoğu zaman bir engel teşkil etmektedir.

Kemoterapi, nüks veya progrese beyin tümörlerinin tedavisinin temeli oluşturmaktadır. Ancak, mevcut rejimler ile sınırlı palyasyon sağlanırken, bu hastala-

<sup>1</sup> Doç. Dr. Cumhuriyet Üniversitesi Tıp Fakültesi Radyasyon Onkolojisi Anabilim Dalı yucelbirsen@yahoo.com

özelliklerine (hacim ve yer), önceki RT doz ve hacim ve hasta özelliklerine (yaş ve performans durumu) bağlıdır. Radyonekroz riski açısından da iki RT ışınlama zamanı ve organın aldığı NTD-k veya kümülatif BED değerlerine dikkat edilmesi gerekmektedir.

**Anahtar Kelimeler:** Nüks Santral Sinir Sistemi Tümörleri, Yeniden ışınlama, Sağkalım.

## KAYNAKLAR

1. Stupp R, Mason WP, van den Bent MJ, et al. European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 2005;352:987-996.
2. Bloch O, Han SJ, Cha S, et al. Impact of extent of resection for recurrent glioblastoma on overall survival: clinical article. *J Neurosurg.* 2012;117:1032-8.
3. Oppenlander ME, Wolf AB, Snyder LA, et al. An extent of resection threshold for recurrent glioblastoma and its risk for neurological morbidity. *J Neurosurg.* 2014;120:846-53.
4. Suchorska B, Weller M, Tabatabai G, et al. Complete resection of contrast-enhancing tumor volume is associated with improved survival in recurrent glioblastoma-results from the DIRE-CTOR trial. *Neuro Oncol.* 2016;18:549-56.
5. Bauman GS, Snead PK, Wara WM, et al. Reirradiation of primary SSS tumors. *Int J Radiat Oncol Biol Phys.* 1996;36:433-41.
6. Palmer JD, Siglin J, Yamoah K, et al. Re-resection for recurrent high-grade glioma in the setting of re-irradiation: more is not always better. *J Neurooncol.* 2015;124:215-21.
7. Veninga T, Langendijk HA, Slotman BJ, et al. Reirradiation of primary brain tumours: Survival, clinical response and prognostic factors. *Radiother Oncol.* 2001;59:127-37.
8. Combs SE, Thilmann C, Edler L, Debus J, et al. Efficacy of fractionated stereotactic reirradiation in recurrent gliomas: long-term results in 172 patients treated in a single institution. *J Clin Oncol.* 2005; 23(34):8863-9.
9. Bartsch R, Weitmann HD, Pennwieser W, et al. Retrospective analysis of re-irradiation in malignant glioma; single-center experience. *Wien Klin Wochenschr.* 2005;117:821-26.
10. Henke G, Paulsen F, Steinbach JP, et al. Hypofractionated reirradiation for recurrent malignant glioma. *Strahlenther Onkol.* 2009;185:113-9.
11. Combs SE, Edler L, Rausch R, et al. Generation and validation of a prognostic score to predict outcome after re-irradiation of recurrent glioma. *Acta Oncol.* 2013;52(1):147-52.
12. Combs SE, Bischof M, Welzel T. Radiochemotherapy with temozolomide as re-irradiation using high precision fractionated stereotactic radiotherapy (FSRT) in patients with recurrent gliomas. *J Neurooncol.* 2008;89:205-10.
13. Scorsetti M, Navarria P, Pessina F, et al. Multimodality therapy approaches, local and systemic treatment, compared with chemotherapy alone in recurrent glioblastoma. *BMC Cancer.* 2015;15:486.
14. Hayat K, Jones B, Bisbrow G, et al. Retreatment of patients with intracranial gliomas by external beam radiotherapy and cytotoxic chemotherapy. *Clin Oncol (R. Coll. Radiol).* 1997; 9:158-63.
15. Arcicasa M, Roncadin M, Bidoli E, et al. Reirradiation and lomustine in patients with relapsed high-grade gliomas. *Int. J. Radiat. Oncol Biol Phys.* 1999;43:789-93.
16. Magnuson W, Robins HI, Mohindra P, et al. Large volume reirradiation as salvage therapy for glioblastoma after progression on bevacizumab. *J Neuro-Oncol.* 2014;117(1):133-9.
17. Shen CJ, Kummerlowe MN, Redmond KJ, et al. Re-irradiation for malignant glioma: Toward patients selection and defining treatment parameters for salvage. *Advances in Radiation Oncology.* 2018;3:582-90.

18. Dincoglan F, Beyzadeoglu M, Sager O, et al. Management of patients with recurrent glioblastoma using hypofractionated stereotactic radiotherapy. *Tumori Journal.* 2015;101(2):179-84.
19. Minniti G, Armosini V, Salvati M, et al. Fractionated stereotactic reirradiation and concurrent temozolamide in patients with recurrent glioblastoma. *J Neuro-Oncol.* 2011; 103(3):683–91.
20. Wong CS and van der Kogel AJ. Mechanisms of radiation injury to the central nervous system: implications for neuroprotection. *Mol Interv.* 2004;4:273-84.
21. Wong CS, Fehlings MG, Sahgal A. Pathobiology of radiation myopathy and strategies to mitigate injury. *Spinal Cord.* 2015;53:574-80
22. Ang KK, Jiang GL, Feng Y, et al. Extent and kinetics of recovery of occult spinal cord injury. *Int J Radiat Oncol Biol Phys.* 2001;50:1013-20.
23. Nieder C, Grosu AL, Andratschke NH, et al. Proposal of human spinal cord reirradiation dose based on collection of data from 40 patients. *Int J Radiat Oncol Biol Phys.* 2005;61:851-5.
24. Mayer R and Sminia P. Reirradiation tolerance of the human brain. *Int J Radiat Oncol Biol Phys.* 2008;70:1350-60.
25. Kessel KA, Hesse J, Straube C, , et al. Validation of an established prognostic score after re-irradiation of recurrent glioma. *Acta Oncologica.* 2017;56(3):422-6.
26. Scoccianti S, Francolinia G, Cartaa GA, et al. Re-irradiation as salvage treatment in recurrent glioblastoma: A comprehensive literature review to provide practical answers to frequently asked questions. *Critical Reviews in Oncology / Hematology.* 2018;126:80-91.
27. Paul S, Sesikaran BN, Patro KC, et al. Re-irradiation in Central Nervous System Tumors. *Journal of Current Oncology.* 2018;1(1):40-2.
28. Nieder C, Nestle U, Ketter R, et al. Hyperfractionated and accelerated-hyperfractionated radiotherapy for glioblastoma multiforme. *Radiat Oncol Investig.* 1999;7:36-41.
29. Wick W, Debus J, Bendszus M, et al. A phase II, randomized, open-label, multi-center study of weekly APG101 + reirradiation versus reirradiation in the treatment of patients with recurrent glioblastoma. *Eur J Cancer.* 2013;49:776.
30. Lee J, Cho J, Chang JH, et al. Re-Irradiation for Recurrent Gliomas: Treatment Outcomes and Prognostic Factors. *Yonsei Med J.* 2016;57(4):824-30.
31. Shepherd SF, Laing RW, Cosgrove VP, et al. Hypofractionated stereotactic radiotherapy in the management of recurrent glioma. *Int J Radiat Oncol Biol Phys.* 1997;37:393–8.
32. Hudes RS, Corn BW, Werner-Wasik M, et al. A phase I dose escalation study of hypofractionated stereotactic radiotherapy as salvage therapy for persistent or recurrent malignant glioma. *International Journal of Radiation Oncology Biology Physics.* 1999;43(2):293-8.
33. Selch MT, DeSalles AAF, Solberg TD, et al. Hypofractionated stereotactic radiotherapy for Recurrent Malignant Gliomas. *J Radiosurg.* 2000;3:3-12.
34. Grosu AL, Weber WA, Franz M, et al. Reirradiation of recurrent high-grade gliomas using amino acid PET (SPECT)/CT/MRI image fusion to determine gross tumor volume for stereotactic fractionated radiotherapy. *Int J Radiat Oncol Biol Phys.* 2005;63:511-9.
35. Vordermark D, Kolbl, O, Ruprecht K, et al. Hypofractionated stereotactic re-irradiation: Treatment option in recurrent malignant glioma. *BMC Cancer.* 2005;5:55.
36. Ernst-Stecken A, Ganslandt O, Lambrecht U, et al. Survival and quality of life after hypofractionated stereotactic radiotherapy for recurrent malignant glioma *J Neurooncol.* 2007;81:287-94.
37. Fokas E, Wacker U, Gross MW, et al. Hypofractionated stereotactic reirradiation of recurrent glioblastomas: a beneficial treatment option after highdose radiotherapy? *Strahlenther Onkol.* 2009;185(4):235-40.
38. Fogh SE, Andrews DW, Glass J, et al. Hypofractionated Stereotactic Radiation Therapy: An Effective Therapy for Recurrent High-Grade Gliomas. *J Clin Oncol.* 2010;28:3048-53.
39. McKenzie JT, Guarnaschelli JN, Vagal AS, et al. Hypofractionated stereotactic radiotherapy for unifocal and multifocal recurrence of malignant gliomas. *Journal of Neuro-oncology.* 2013;113(3):403-9.
40. Ogura K, Mizowaki T, Arakawa Y, et al. Efficacy of salvage stereotactic radiotherapy for recurrent glioma: impact of tumor morphology and method of target delineation on local control. *Cancer Medicine.* 2013;2(6):942-9.

41. Yazici G, Cengiz M, Ozyigit G, et al. Hypofractionated stereotactic reirradiation for recurrent glioblastoma. *Journal of Neuro-oncology*. 2014;120(1):117-23.
42. Navarría P, Ascolese AM, Tomatis S, et al. Hypofractionated stereotactic radiation therapy in recurrent high-grade glioma: a new challenge. *Cancer Research and Treatment*. 2016;48(1):37-44.
43. Alexander III E and Loeffler JS. Radiosurgery using a modified linear accelerator. *Neurosurgery Clinics of North America*. 1992;3(1):167-90.
44. Shrieve DC, Alexander III E, Wen PY, et al. Comparison of stereotactic radiosurgery and brachytherapy in the treatment of recurrent glioblastoma multiforme. *Neurosurgery*. 1995;36:275-84.
45. Larson DA, Gutin PH, McDermott M, et al. Gamma knife for glioma: Selection factors and survival. *Int J Radiat Oncol Biol Phys*. 1996;36:1045-53.
46. Kondziolka D, Flickinger J, Jonh C, et al. Survival benefit of stereotactic radiosurgery for patients with malignant glial neoplasm. *Neurosurgery*. 1997;41:776-785.
47. Cho KH, Hall WA, Gerbi BJ, et al. Single dose versus fractionated stereotactic radiotherapy for recurrent high-grade gliomas. *Int J Radiat Oncol Biol Phys*. 1999;45:1133-141.
48. Hsieh, PC, Chandler JP, Bhangoo S, et al. Adjuvant gamma knife stereotactic radiosurgery at the time of tumor progression potentially improves survival for patients with glioblastoma multiforme. *Neurosurgery*. 2005;57:684-691.
49. Kong DS, Lee JI, Park K, et al. Efficacy of stereotactic radiosurgery as a salvage treatment for recurrent malignant gliomas. *Cancer*. 2008;112: 2046-2051.
50. Biswas T, Okunieff P, Schell MC, et al. Stereotactic radiosurgery for glioblastoma: Retrospective analysis. *Radiat Oncol*. 2009;4:1-11.
51. Patel M, Siddiqui F, Jin JY, et al. Salvage reirradiation for recurrent glioblastoma with radiosurgery: Radiographic response and improved survival. *J Neurooncol*. 2009;92:185-191.
52. Maranzano E, Anselmo P, Casale M, et al. Treatment of recurrent glioblastoma with stereotactic radiotherapy: Long-term results of a mono-institutional trial. *Tumori*. 2011;97: 56-61.
53. Cuneo KC, Vredenburgh JJ, Sampson JH, et al. Safety and efficacy of stereotactic radiosurgery and adjuvant bevacizumab in patients with recurrent malignant gliomas. *Int J Radiat Oncol Biol Phys*. 2012;82: 2018-2024.
54. Cabrera AR, Cuneo KC, Desjardins A, et al: Concurrent stereotactic radiosurgery and bevacizumab in recurrent malignant gliomas: A prospective trial. *Int J Radiat Oncol Biol Phys*. 2013;86: 873-879.
55. Martínez-Carrillo M, Tovar-Martín I, Zurita-Herrera M, et al. Salvage radiosurgery for selected patients with recurrent malignant gliomas. *BioMed Research International*. 2014: ID:657953:1-10.
56. Gabayan AJ, Green SB, Sanan A, et al. GliaSite brachytherapy for treatment of recurrent malignant gliomas: A retrospective multi-institutional analysis. *Neurosurgery*. 2006;58:701-709.
57. Tsvelis N, Kolotas C, Birn G, et al. CT-guided interstitial HDR brachytherapy for recurrent glioblastoma multiforme. Long-term results. *Strahlenther Onkol*. 2007;183:563-570.
58. Darakchiev BJ, Albright RE, Breneman JC, et al. Safety and efficacy of permanent iodine-125 seed implants and carmustine wafers in patients with recurrent glioblastoma multiforme. *J Neurosurg*. 2008;108:236-242.
59. Fabrini MG, Perrone F, De Franco L, et al. Perioperative high-dose-rate brachytherapy in the treatment of recurrent malignant gliomas. *Strahlenther Onkol*. 2009;185:524-529.
60. Archavlis E, Tsvelis N, Birn G, et al. Survival analysis of HDR brachytherapy versus reoperation versus temozolamide alone: A retrospective cohort analysis of recurrent glioblastoma multiforme. *BMJ Open*. 2013;3:e002262,
61. Kickingereder P, Hamisch C, Suchorska B, Galldiks N, et al. Low-dose rate stereotactic iodine-125 brachytherapy for the treatment of inoperable primary and recurrent glioblastoma: Single-center experience with 201 cases. *J Neurooncol*. 2013;120:615-623.

62. Wick A, Pasher C, Wick Wet al. Rechallenge with temozolomide in patients with recurrent gliomas. *J. Neurol.* 2009;256:734-741.
63. Yung WK, Prados MD, Yaya-Tur R, et al. Multicentre phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. Temodal Brain Tumour Group. *J Clin Oncol.* 1999;17:2762-2771.
64. Wick W, Wller M, Weiler M, et al. Pathway inhibition: Emerging molecular targets for treating glioblastoma. *Neuro-Oncology.* 2011;13:566-579.
65. Lobon MJ, Bautista F, Riet F, et al. Re-irradiation of recurrent pediatric ependymoma: modalities and outcomes: a twenty-year survey. *Springer Plus.* 2016;5:879.
66. Rogers L, Pueschel J, Spetzler R, et al. Is gross-total resection sufficient treatment for posterior fossa ependymomas? *J Neurosurg.* 2005;102:629-636.
67. Straube C, Elpula G, Gempt J, et al. Re-irradiation after gross total resection of recurrent glioblastoma. *Strahlenther Onkol.* 2017;352:1-13.
68. Nava F, Tramacere I, Fittipaldo A, et al. Survival effect of first- and second-line treatments for patients with primary glioblastoma: a cohort study from a prospective registry, 1997-2010. *Neuro-Oncology.* 2014;16(5):719-727.
69. Niyazi M, Brada M, Chalmers AJ, et al. ESTROACROP guideline “target delineation of glioblastomas”. *Radiother Oncol.* 2016;118:35-42.
70. Heinemann F, Schwaiger M, Molls M, et al. An interindividual comparison of O-(2-[<sup>18</sup>F] fluoroethyl)L-tyrosine (FET)- and L-[methyl-<sup>11</sup>C] methionine (MET)-PET in patients with brain gliomas and metastases. *Int J Radiat Oncol Biol Phys.* 2011;81:1049-1058.
71. Ho ALK and Jena R. Re-irradiation in the brain: Primary gliomas. *Clinical Oncology.* 2018;30:124-136.
72. Wang HZ, Luo JW, Yi JL, et al. The tolerance of brainstem in reirradiation with intensity modulated radiation therapy in recurrent nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Physics.* 2016;96:E340.
73. Mayo C, Martel MK, Marks LB, et al. Radiation dose-volume effects of optic nerves and chiasm. *Int J Radiat Oncol Biol Phys.* 2010;76:28-35.