

BÖLÜM 38

Pediatrik Hastaların Radyoterapisinde Radyasyon Maruziyetinin Gelecekteki Sorunları



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GİRİŞ

Kanser hastalarının tedavisi geçmişten günümüze gelişen yeni kemoterapötik ajanlar, radyoterapi (RT) ve cerrahının farklı kombinasyonlarıyla elde edilen daha iyi klinik yanıtlarla oldukça değişmiş ve gelişmiştir. Elde edilen sağkalım avantajları hem multimodal yaklaşılara hem de RT'deki teknolojik gelişmelere bağlıdır. Bu gelişmeler tüm kanser hastalarında patolojik ve anatomik bölgeye göre değişmekte birlikte önemli sağkalım katkıları sağlamıştır. Bu durumda tamamen kür sağlanan hastalarda önem kazanan konu; tedaviye bağlı geç yan etkiler olmuştur. Erişkin kanserlerinde bu etkiler daha kontrol edilebilir düzeyde olmakla birlikte pediatrik hastalarda daha kritik bir öneme sahiptir.

Yarım yüzyıl öncesine kadar pediatrik hastalarındaki sağkalımlar gelişmiş ülkelerde dahi % 50'den az iken günümüzde kür oranları % 85 civarındadır (1, 2). Her 6 hastadan birinin yaşamını normal olarak sürdürüp tamamlayacağı düşünüldüğünde; bu hastaların erişkinlere göre daha uzun yaşam

süreleri nedeniyle gelecekte daha fazla sorunla baş etmek zorunda kalacakları aşikardır. Hipokratin önce zarar verme prensibinin, konu çocuk olunca; biz hekimleri ne kadar da çok zorlayacağı ortadadır. Ancak bu durum tedavi planlama ve uygulamada daha titiz ve incelikli bir yaklaşımın da yolunu açmaktadır.

Bu yazının amacı da çocukluk çağı kanserlerine bilimsel veriler ışığında radyasyon onkologu gözüyle bakmak ve 5 yıllık sağkalımı değil, 70-80 yıllık sağlıklı kalımı önceleyecek bakış açısınıがらştırmaktır.

PEDIATRİK HASTALARDA RADYOTERAPİ

Her ne kadar tedavi protokollerinde mümkün olduğunca daha az yer olması tercih edilse de önemli bir grup hastada radyasyon tedavisi olmaksızın kür sağlanamamaktadır. Pediatrik onkolojik tədavilerde erişkinlerden farklı olarak RT'nin geç yan etkileri oldukça önemlidir. Bu durum radyasyon onkologlarına hem tedavi hem de destekleyici yak-

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- Nörokognitif bozukluk kranial RT'nin en sık geç dönem yan etkilerinden biridir.
- Çocukluk çağında kanserlerinde baş-boyun ve beyin tümörlerinin RT'sinde hipotalamo-pituiter eksenin işinlanması birtakım nöroendokrin bozukluklara neden olabilir.
- Radyasyona bağlı geç orbital komplikasyonlar sıklıkla görülebilir.
- RT'nin kardiyak disfonksiyona sebep olabileceği, özellikle de 5 Gy üzerindeki RT dozlarının riski belirgin artıldığı gösterilmiştir.
- Çocukluk çağında kanserlerinden kür sağlanan hastalarda ikincil kanser oranı normal popülasyona göre 6 kat fazladır.

KAYNAKLAR

1. Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. *CA Cancer J Clin.* 2010;60(5):277-300.
2. Ries LG, Pollack ES, Young JL, Jr. Cancer patient survival: Surveillance, Epidemiology, and End Results Program, 1973-79. *J Natl Cancer Inst.* 1983;70(4):693-707.
3. Hudson MM, Neglia JP, Woods WG, et al. Lessons from the past: opportunities to improve childhood cancer survivor care through outcomes investigations of historical therapeutic approaches for pediatric hematological malignancies. *Pediatr Blood Cancer.* 2012;58(3):334-343.
4. Armstrong GT, Chen Y, Yasui Y, et al. Reduction in Late Mortality among 5-Year Survivors of Childhood Cancer. *N Engl J Med.* 2016;374(9):833-842.
5. Armstrong GT, Kawashima T, Leisenring W, et al. Aging and risk of severe, disabling, life-threatening, and fatal events in the childhood cancer survivor study. *J Clin Oncol.* 2014;32(12):1218-1227.
6. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med.* 2006;355(15):1572-1582.
7. Hudson MM, Ness KK, Gurney JG, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. *Jama.* 2013;309(22):2371-2381.
8. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys.* 1991;21(1):109-122.
9. Marks LB, Ten Haken RK, Martel MK. Guest editor's introduction to QUANTEC: a users guide. *Int J Radiat Oncol Biol Phys.* 2010;76(3 Suppl):S1-2.
10. Constine LS, Ronckers CM, Hua CH, et al. Pediatric Normal Tissue Effects in the Clinic (PENTEC): An International Collaboration to Analyse Normal Tissue Radiation Dose-Volume Response Relationships for Paediatric Cancer Patients. *Clin Oncol (R Coll Radiol).* 2019;31(3):199-207.
11. Nathan PC, Patel SK, Dilley K, et al. Guidelines for identification of, advocacy for, and intervention in neurocognitive problems in survivors of childhood cancer: a report from the Children's Oncology Group. *Arch Pediatr Adolesc Med.* 2007;161(8):798-806.
12. Ellenberg L, Liu Q, Gioia G, et al. Neurocognitive status in long-term survivors of childhood CNS malignancies: a report from the Childhood Cancer Survivor Study. *Neuropsychology.* 2009;23(6):705-717.
13. Reeves CB, Palmer SL, Reddick WE, et al. Attention and memory functioning among pediatric patients with medulloblastoma. *J Pediatr Psychol.* 2006;31(3):272-280.
14. Khan RB, Hudson MM, Ledet DS, et al. Neurologic morbidity and quality of life in survivors of childhood acute lymphoblastic leukemia: a prospective cross-sectional study. *J Cancer Surviv.* 2014;8(4):688-696.
15. Robinson KE, Kuttesch JF, Champion JE, et al. A quantitative meta-analysis of neurocognitive sequelae in survivors of pediatric brain tumors. *Pediatr Blood Cancer.* 2010;55(3):525-531.
16. Butler RW, Fairclough DL, Katz ER, et al. Intellectual functioning and multi-dimensional attentional processes in long-term survivors of a central nervous system related pediatric malignancy. *Life Sci.* 2013;93(17):611-616.
17. Mulhern RK, Merchant TE, Gajjar A, et al. Late neurocognitive sequelae in survivors of brain tumours in childhood. *Lancet Oncol.* 2004;5(7):399-408.
18. Mulhern RK, White HA, Glass JO, et al. Attentional functioning and white matter integrity among survivors of malignant brain tumors of childhood. *J Int Neuropsychol Soc.* 2004;10(2):180-189.
19. Briere ME, Scott JG, McNall-Knapp RY, et al. Cognitive outcome in pediatric brain tumor survivors: delayed attention deficit at long-term follow-up. *Pediatr Blood Cancer.* 2008;50(2):337-340.
20. Mabbott DJ, Spiegler BJ, Greenberg ML, et al. Serial evaluation of academic and behavioral outcome after treatment with cranial radiation in childhood. *J Clin Oncol.* 2005;23(10):2256-2263.
21. Edelstein K, Spiegler BJ, Fung S, et al. Early aging in adult survivors of childhood medulloblastoma: long-term neurocognitive, functional, and physical outcomes. *Neuro Oncol.* 2011;13(5):536-545.
22. Palmer SL, Goloubeva O, Reddick WE, et al. Patterns of intellectual development among survivors of pediatric medulloblastoma: a longitudinal analysis. *J Clin Oncol.* 2001;19(8):2302-2308.
23. Merchant TE, Schreiber JE, Wu S, et al. Critical combinations of radiation dose and volume predict intelligence quotient and academic achievement



- scores after craniospinal irradiation in children with medulloblastoma. *Int J Radiat Oncol Biol Phys.* 2014;90(3):554-561.
24. Reimers TS, Ehrenfels S, Mortensen EL, et al. Cognitive deficits in long-term survivors of childhood brain tumors: Identification of predictive factors. *Med Pediatr Oncol.* 2003;40(1):26-34.
 25. Armstrong GT, Conklin HM, Huang S, et al. Survival and long-term health and cognitive outcomes after low-grade glioma. *Neuro Oncol.* 2011;13(2):223-234.
 26. Ris MD, Walsh K, Wallace D, et al. Intellectual and academic outcome following two chemotherapy regimens and radiotherapy for average-risk medulloblastoma: COG A9961. *Pediatr Blood Cancer.* 2013;60(8):1350-1357.
 27. Orgel E, O'Neil SH, Kayser K, et al. Effect of Sensorineural Hearing Loss on Neurocognitive Functioning in Pediatric Brain Tumor Survivors. *Pediatr Blood Cancer.* 2016;63(3):527-534.
 28. Di Pinto M, Conklin HM, Li C, et al. Learning and memory following conformal radiation therapy for pediatric craniopharyngioma and low-grade glioma. *Int J Radiat Oncol Biol Phys.* 2012;84(3):e363-369.
 29. Bowers DC, Liu Y, Leisenring W, et al. Late-occurring stroke among long-term survivors of childhood leukemia and brain tumors: a report from the Childhood Cancer Survivor Study. *J Clin Oncol.* 2006;24(33):5277-5282.
 30. Nassar SL, Conklin HM, Zhou Y, et al. Neurocognitive outcomes among children who experienced seizures during treatment for acute lymphoblastic leukemia. *Pediatr Blood Cancer.* 2017;64(8).
 31. Moyer KH, Willard VW, Gross AM, et al. The impact of attention on social functioning in survivors of pediatric acute lymphoblastic leukemia and brain tumors. *Pediatr Blood Cancer.* 2012;59(7):1290-1295.
 32. Brinkman TM, Palmer SL, Chen S, et al. Parent-reported social outcomes after treatment for pediatric embryonal tumors: a prospective longitudinal study. *J Clin Oncol.* 2012;30(33):4134-4140.
 33. Mitby PA, Robison LL, Whitton JA, et al. Utilization of special education services and educational attainment among long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Cancer.* 2003;97(4):1115-1126.
 34. Kunin-Batson A, Kadan-Lottick N, Zhu L, et al. Predictors of independent living status in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Pediatr Blood Cancer.* 2011;57(7):1197-1203.
 35. Janson C, Leisenring W, Cox C, et al. Predictors of marriage and divorce in adult survivors of childhood cancers: a report from the Childhood Cancer Survivor Study. *Cancer Epidemiol Biomarkers Prev.* 2009;18(10):2626-2635.
 36. Vinchon M, Baroncini M, Leblond P, et al. Morbidity and tumor-related mortality among adult survivors of pediatric brain tumors: a review. *Childs Nerv Syst.* 2011;27(5):697-704.
 37. Ramelli GP, von der Weid N, Stanga Z, et al. Suprasellar germinomas in childhood and adolescence: diagnostic pitfalls. *J Pediatr Endocrinol Metab.* 1998;11(6):693-697.
 38. Fahrner B, Prosch H, Minkov M, et al. Long-term outcome of hypothalamic pituitary tumors in Langerhans cell histiocytosis. *Pediatr Blood Cancer.* 2012;58(4):606-610.
 39. Merchant TE, Goloubeva O, Pritchard DL, et al. Radiation dose-volume effects on growth hormone secretion. *Int J Radiat Oncol Biol Phys.* 2002;52(5):1264-1270.
 40. Merchant TE, Rose SR, Bosley C, et al. Growth hormone secretion after conformal radiation therapy in pediatric patients with localized brain tumors. *J Clin Oncol.* 2011;29(36):4776-4780.
 41. Nandagopal R, Laverdière C, Mulrooney D, et al. Endocrine late effects of childhood cancer therapy: a report from the Children's Oncology Group. *Horm Res.* 2008;69(2):65-74.
 42. Rose SR, Danish RK, Kearney NS, et al. ACTH deficiency in childhood cancer survivors. *Pediatr Blood Cancer.* 2005;45(6):808-813.
 43. Kazlauskaitė R, Evans AT, Villabona CV, et al. Corticotropin tests for hypothalamic-pituitary-adrenal insufficiency: a metaanalysis. *J Clin Endocrinol Metab.* 2008;93(11):4245-4253.
 44. Raney RB, Anderson JR, Kollath J, et al. Late effects of therapy in 94 patients with localized rhabdomyosarcoma of the orbit: Report from the Intergroup Rhabdomyosarcoma Study (IRS)-III, 1984-1991. *Med Pediatr Oncol.* 2000;34(6):413-420.
 45. Qaddoumi I, Bass JK, Wu J, et al. Carboplatin-associated ototoxicity in children with retinoblastoma. *J Clin Oncol.* 2012;30(10):1034-1041.
 46. Hua C, Bass JK, Khan R, et al. Hearing loss after radiotherapy for pediatric brain tumors: effect of cochlear dose. *Int J Radiat Oncol Biol Phys.* 2008;72(3):892-899.
 47. Bhandare N, Jackson A, Eisbruch A, et al. Radiation therapy and hearing loss. *Int J Radiat Oncol Biol Phys.* 2010;76(3 Suppl):S50-57.
 48. Kline LB, Kim JY, Ceballos R. Radiation optic neuropathy. *Ophthalmology.* 1985;92(8):1118-1126.
 49. Paulino AC, Simon JH, Zhen W, et al. Long-term effects in children treated with radiotherapy for head and neck rhabdomyosarcoma. *Int J Radiat Oncol Biol Phys.* 2000;48(5):1489-1495.
 50. Oberlin O, Rey A, Anderson J, et al. Treatment of orbital rhabdomyosarcoma: survival and late effects of treatment—results of an international workshop. *J Clin Oncol.* 2001;19(1):197-204.



51. Chodick G, Sigurdson AJ, Kleinerman RA, et al. The Risk of Cataract among Survivors of Childhood and Adolescent Cancer: A Report from the Childhood Cancer Survivor Study. *Radiat Res.* 2016;185(4):366-374.
52. Lipshultz SE, Adams MJ, Colan SD, et al. Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: pathophysiology, course, monitoring, management, prevention, and research directions: a scientific statement from the American Heart Association. *Circulation.* 2013;128(17):1927-1995.
53. Tukenova M, Guibout C, Oberlin O, et al. Role of cancer treatment in long-term overall and cardiovascular mortality after childhood cancer. *J Clin Oncol.* 2010;28(8):1308-1315.
54. Reulen RC, Winter DL, Frobisher C, et al. Long-term cause-specific mortality among survivors of childhood cancer. *Jama.* 2010;304(2):172-179.
55. Mertens AC, Liu Q, Neglia JP, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 2008;100(19):1368-1379.
56. Kero AE, Järvelä LS, Arola M, et al. Cardiovascular morbidity in long-term survivors of early-onset cancer: a population-based study. *Int J Cancer.* 2014;134(3):664-673.
57. Hahn E, Jiang H, Ng A, et al. Late Cardiac Toxicity After Mediastinal Radiation Therapy for Hodgkin Lymphoma: Contributions of Coronary Artery and Whole Heart Dose-Volume Variables to Risk Prediction. *Int J Radiat Oncol Biol Phys.* 2017;98(5):1116-1123.
58. Mulrooney DA, Yeazel MW, Kawashima T, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *Bmj.* 2009;339:b4606.
59. Henson KE, Reulen RC, Winter DL, et al. Cardiac Mortality Among 200 000 Five-Year Survivors of Cancer Diagnosed at 15 to 39 Years of Age: The Teenage and Young Adult Cancer Survivor Study. *Circulation.* 2016;134(20):1519-1531.
60. Bates JE, Howell RM, Liu Q, et al. Therapy-Related Cardiac Risk in Childhood Cancer Survivors: An Analysis of the Childhood Cancer Survivor Study. *J Clin Oncol.* 2019;37(13):1090-1101.
61. Armenian SH, Hudson MM, Mulder RL, et al. Recommendations for cardiomyopathy surveillance for survivors of childhood cancer: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. *Lancet Oncol.* 2015;16(3):e123-136.
62. Haddy N, Diallo S, El-Fayech C, et al. Cardiac Diseases Following Childhood Cancer Treatment: Cohort Study. *Circulation.* 2016;133(1):31-38.
63. van der Pal HJ, van Dalen EC, van Delden E, et al. High risk of symptomatic cardiac events in childho-
- od cancer survivors. *J Clin Oncol.* 2012;30(13):1429-1437.
64. Bhakta N, Liu Q, Ness KK, et al. The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE). *Lancet.* 2017;390(10112):2569-2582.
65. Bhakta N, Liu Q, Yeo F, et al. Cumulative burden of cardiovascular morbidity in paediatric, adolescent, and young adult survivors of Hodgkin's lymphoma: an analysis from the St Jude Lifetime Cohort Study. *Lancet Oncol.* 2016;17(9):1325-1334.
66. Mulrooney DA, Soliman EZ, Ehrhardt MJ, et al. Electrocardiographic abnormalities and mortality in aging survivors of childhood cancer: A report from the St Jude Lifetime Cohort Study. *Am Heart J.* 2017;189:19-27.
67. Armstrong GT, Oeffinger KC, Chen Y, et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. *J Clin Oncol.* 2013;31(29):3673-3680.
68. Stewart FA, Akleyev AV, Hauer-Jensen M, et al. ICRP publication 118: ICRP statement on tissue reactions and early and late effects of radiation in normal tissues and organs--threshold doses for tissue reactions in a radiation protection context. *Ann ICRP.* 2012;41(1-2):1-322.
69. Goldsby R, Chen Y, Raber S, et al. Survivors of childhood cancer have increased risk of gastrointestinal complications later in life. *Gastroenterology.* 2011;140(5):1464-1471.e1461.
70. Skou AS, Glosli H, Jahnukainen K, et al. Renal, gastrointestinal, and hepatic late effects in survivors of childhood acute myeloid leukemia treated with chemotherapy only—a NOPHO-AML study. *Pediatr Blood Cancer.* 2014;61(9):1638-1643.
71. Dawson LA, Kavanagh BD, Paulino AC, et al. Radiation-associated kidney injury. *Int J Radiat Oncol Biol Phys.* 2010;76(3 Suppl):S108-115.
72. McDonald S, Rubin P, Phillips TL, et al. Injury to the lung from cancer therapy: clinical syndromes, measurable endpoints, and potential scoring systems. *Int J Radiat Oncol Biol Phys.* 1995;31(5):1187-1203.
73. McDonald S, Rubin P, Maasilta P. Response of normal lung to irradiation. Tolerance doses/tolerance volumes in pulmonary radiation syndromes. *Front Radiat Ther Oncol.* 1989;23:255-276; discussion 299-301.
74. Hua C, Hoth KA, Wu S, et al. Incidence and correlates of radiation pneumonitis in pediatric patients with partial lung irradiation. *Int J Radiat Oncol Biol Phys.* 2010;78(1):143-149.
75. Shnorhavorian M, Friedman DL, Koyle MA. Genitourinary long-term outcomes for childhood cancer survivors. *Curr Urol Rep.* 2009;10(2):134-137.
76. Bölling T, Ernst I, Pape H, et al. Dose-volume analysis of radiation nephropathy in children: preliminary



- report of the risk consortium. *Int J Radiat Oncol Biol Phys.* 2011;80(3):840-844.
77. Ritchey ML, Green DM, Thomas PR, et al. Renal failure in Wilms' tumor patients: a report from the National Wilms' Tumor Study Group. *Med Pediatr Oncol.* 1996;26(2):75-80.
78. Green DM. 11th International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer. Forward. *Pediatr Blood Cancer.* 2012;58(1):111.
79. Paulino AC, Wen BC, Brown CK, et al. Late effects in children treated with radiation therapy for Wilms' tumor. *Int J Radiat Oncol Biol Phys.* 2000;46(5):1239-1246.
80. Krasin MJ, Wiese KM, Spunt SL, et al. Jaw dysfunction related to pterygoid and masseter muscle dosimetry after radiation therapy in children and young adults with head-and-neck sarcomas. *Int J Radiat Oncol Biol Phys.* 2012;82(1):355-360.
81. Hogeboom CJ, Grosser SC, Guthrie KA, et al. Stature loss following treatment for Wilms tumor. *Med Pediatr Oncol.* 2001;36(2):295-304.
82. Wagner LM, Neel MD, Pappo AS, et al. Fractures in pediatric Ewing sarcoma. *J Pediatr Hematol Oncol.* 2001;23(9):568-571.
83. Paulino AC. Late effects of radiotherapy for pediatric extremity sarcomas. *Int J Radiat Oncol Biol Phys.* 2004;60(1):265-274.
84. Friedman DL, Whitton J, Leisenring W, et al. Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 2010;102(14):1083-1095.
85. Hawkins MM, Wilson LM, Burton HS, et al. Radiotherapy, alkylating agents, and risk of bone cancer after childhood cancer. *J Natl Cancer Inst.* 1996;88(5):270-278.
86. Newton WA, Jr., Meadows AT, Shimada H, et al. Bone sarcomas as second malignant neoplasms following childhood cancer. *Cancer.* 1991;67(1):193-201.
87. Cohen RJ, Curtis RE, Inskip PD, et al. The risk of developing second cancers among survivors of childhood soft tissue sarcoma. *Cancer.* 2005;103(11):2391-2396.
88. Turcotte LM, Whitton JA, Friedman DL, et al. Risk of Subsequent Neoplasms During the Fifth and Sixth Decades of Life in the Childhood Cancer Survivor Study Cohort. *J Clin Oncol.* 2015;33(31):3568-3575.
89. Bright CJ, Reulen RC, Winter DL, et al. Risk of subsequent primary neoplasms in survivors of adolescent and young adult cancer (Teenage and Young Adult Cancer Survivor Study): a population-based, cohort study. *Lancet Oncol.* 2019;20(4):531-545.
90. Milano MT, Li H, Gail MH, et al. Long-term survival among patients with Hodgkin's lymphoma who developed breast cancer: a population-based study. *J Clin Oncol.* 2010;28(34):5088-5096.
91. Guérin S, Hawkins M, Shamsaldin A, et al. Treatment-adjusted predisposition to second malignant neoplasms after a solid cancer in childhood: a case-control study. *J Clin Oncol.* 2007;25(19):2833-2839.
92. Pui CH, Ribeiro RC, Hancock ML, et al. Acute myeloid leukemia in children treated with epipodophyllotoxins for acute lymphoblastic leukemia. *N Engl J Med.* 1991;325(24):1682-1687.
93. Bhatia S, Yasui Y, Robison LL, et al. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. *J Clin Oncol.* 2003;21(23):4386-4394.
94. Palmer JD, Tsang DS, Tinkle CL, et al. Late effects of radiation therapy in pediatric patients and survivorship. *Pediatr Blood Cancer.* 2021;68 Suppl 2:e28349.
95. Brodin NP, Munck Af Rosenschöld P, Aznar MC, et al. Radiobiological risk estimates of adverse events and secondary cancer for proton and photon radiation therapy of pediatric medulloblastoma. *Acta Oncol.* 2011;50(6):806-816.
96. Brodin NP, Vogelius IR, Maraldo MV, et al. Life years lost--comparing potentially fatal late complications after radiotherapy for pediatric medulloblastoma on a common scale. *Cancer.* 2012;118(21):5432-5440.
97. Eaton BR, MacDonald SM, Yock TI, et al. Secondary Malignancy Risk Following Proton Radiation Therapy. *Front Oncol.* 2015;5:261.