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The Risk of Radiation Necrosis in Patients with Renal Cell Carcinoma Brain Metastases Treated with Concurrent Administration of Checkpoint Inhibitors and Stereotactic Radiosurgery: An International Cooperative Group Study

Eric J. Lehrer [1] , Jason Gurewitz [2] , Kenneth Bernstein [2] , Dev Patel [3] , Douglas Kondziolka [4] , Ajay Niranjan [5] , Zhishuo Wei [6] , L. Dade Lunsford [7] , Timothy D. Malouff [8] , Henry Ruiz Garcia [9] , Samir Patel [10] , Phillip A. Bonney [11] , Lindsay Hwang [12] , Chang Yu [13] , Gabriel Zada [11] , David Mathieu [14] , Claire Trudel [15] , Rahul N. Prasad [16] , Joshua D. Palmer [17] , Brianna M. Jones [18] , Sonam Sharma [19] , Kareem R. Fakhoury [20] , Chad G. Rusthoven [21] , Christopher P. Deibert [22] , Piero Picozzi [23] , Andrea Franzini [24] , Luca Attuati [24] , Cheng-chia Lee [25] , Huai-che Yang [26] , Manmeet S. Ahluwalia [27] , Jason Sheehan [28] , Daniel M. Trifiletti [8]

1. Department of Radiation Oncology, Ichan School of Medicine at Mount Sinai, New York, USA 2. Department of Radiation Oncology, NYU Langone Medical Center, New York, USA 3. Neurosurgery, NYU Langone Medical Center, New York, USA 4. Department of Neurosurgery, NYU Langone Medical Center, New York, USA 5. Neurosurgery, University Of Pittsburgh, Pittsburgh, USA 6. Neurosurgery, University of Pittsburgh School of Medicine, Pittsburgh, USA 7. Department of Neurological Surgery, University of Pittsburgh, Pittsburgh, USA 8. Department of Radiation Oncology, Mayo Clinic, Jacksonville, USA 9. Radiation Oncology and Neurosurgery, Mayo Clinic, Jacksonville, USA 10. Radiation Oncology, University of Alberta, Alberta, CAN 11. Department of Neurosurgery, University of Southern California, Los Angeles, USA 12. Radiation Oncology, University of Southern California, Los Angeles, USA 13. Neurosurgery, University of Southern California, Los Angeles, USA 14. Neurosurgery, Université de Sherbrooke, Sherbrooke, CAN 15. Internal Medicine, Université de Sherbrooke, Sherbrooke, CAN 16. Department of Radiation Oncology, The Ohio State University Comprehensive Cancer Center-Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, USA 17. Radiation Oncology, The Ohio State University Comprehensive Cancer Center, Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, USA 18. Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, USA 19. Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York City, USA 20. Radiation Oncology, University of Colorado, Denver, USA 21. Department of Radiation Oncology, University of Colorado, Denver, USA 22. Neurosurgery, Emory University School of Medicine, Atlanta, USA 23. Department of Neurosurgery, Humanitas Clinical and Research Center, Milano, ITA 24. Neurosurgery, Humanitas Clinical and Research Center - IRCCS, Milano, ITA 25. Department of Neurosurgery, Taipei Veterans Genenral Hospital, Taipei, TWN 26. Neurosurgery, Taipei Veterans General Hospital, Taipei, TWN 27. Department of Medical Oncology, Miami Cancer Institute, Miami, USA 28. Neurological Surgery, University of Virginia, Charlottesville , USA

Corresponding author: Eric J. Lehrer, ericjlehrer@gmail.com

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Abstract

Objective: Patients with renal cell carcinoma brain metastases are frequently treated with a bimodality regimen consisting of immune checkpoint inhibitors (ICI) and stereotactic radiosurgery (SRS). Multiple single institution retrospective studies have suggested this therapy to be both safe and effective with improved overall survival (OS) with concurrent therapy (SRS and ICI administered within 4 weeks of one another). However, those studies were largely limited to other tumor histologies, and data regarding the risk of development of radiation necrosis are markedly limited. We hypothesized that SRS and ICI may be administered concurrently without an increased risk of developing radiation necrosis.

Methods: This analysis was approved by the International Radiosurgery Research Foundation. Radiation necrosis was evaluated using the CTCAE 5.0 toxicity grading system. Rates of any grade radiation necrosis and symptomatic radiation necrosis (Grade 2+) were compared for concurrent and non-concurrent therapy using the chi-square test. Univariate logistic regression was used to identify factors associated with an increased risk of developing radiation necrosis of any grade. The Kaplan Meier method and log-rank test were used to compare 1-year OS and 1-year local control (LC) for the concurrent and non-concurrent groups, where the null-hypothesis was rejected for $p<0.05$.

Results: There were 50 patients included in the analysis with 382 brain metastases across 7 international institutions. The median follow-up was 12.1 months; median age was 65 years (range: 49-85 years). Active extracranial disease was present in 86% of patients. The median Karnofsky Performance Status (KPS) was 80. The median margin dose was 20 Gy prescribed to the 50% isodose line. All patients were treated with single fraction SRS and 4% underwent prior whole brain radiation therapy (WBRT). The median treated tumor volume was 3.32 cm3 (range: 0.06-42.38 cm3). The median V12 was 8.42 cm3 (range: 0.27-111.22 cm3).

Radiation necrosis of any grade occurred in 17.4% and 21.9% of patients in the concurrent and non-concurrent groups, respectively (p=0.17). Symptomatic radiation necrosis occurred in 4.3% and 12.5% of patients in the concurrent and non-concurrent groups, respectively (p=0.30). On univariate logistic regression, volume of irradiated brain during SRS (OR: 1.08; 95% CI: 1.01-1.19; p=0.04) was associated with an increased risk of developing radiation necrosis and a trend was observed for increasing V12 (OR: 1.03; 95% CI: 0.99-1.06; p=0.06). The use of concurrent therapy (OR: 0.74; 95% CI: 0.17-2.30; p=0.76), KPS (OR: 0.96; 95% CI: 0.90-1.02; p=0.19), prior WBRT (OR: 0.23; 95% CI: 0.01-6.20; p=0.32), and immune checkpoint inhibitor agent were not significant predictors of radiation necrosis. The 1-year OS was 71.9% and 84.9% for the concurrent and non-concurrent groups, respectively (p=0.09). The 1-year LC was 90.9% and 96.3% for the concurrent and non-concurrent groups, respectively (p=0.45).

Conclusion: Concurrent administration of ICI and SRS in patients with renal cell carcinoma brain metastases does not increase the risk of development of radiation necrosis when compared to non-concurrent therapy. Attempts to minimize V12 and consideration of fractionated radiosurgery in patients with higher volume disease are acceptable strategies to mitigate this risk. Prospective data are needed to further validate these findings.