



**University of
Zurich**^{UZH}

**Zurich Open Repository and
Archive**

University of Zurich
Main Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2014

The vanishing role of whole brain radiotherapy for primary central nervous system lymphoma

Weller, M

DOI: <https://doi.org/10.1093/neuonc/nou120>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-98100>

Journal Article

Accepted Version

Originally published at:

Weller, M (2014). The vanishing role of whole brain radiotherapy for primary central nervous system lymphoma. *Neuro-Oncology*, 16(8):1035-1036.

DOI: <https://doi.org/10.1093/neuonc/nou120>

POINT/COUNTERPOINT

The vanishing role of whole brain radiotherapy for primary central nervous system lymphoma

Michael Weller, MD

Department of Neurology

University Hospital Zurich

Frauenklinikstrasse 26

CH-8091 Zurich

Tel. 41 44 255 5500

Fax 41 44 255 4507

E-Mail michael.weller@usz.ch

To estimate the value of whole brain radiotherapy (WBRT) in the treatment of primary CNS lymphoma (PCNSL), it is important to recall the goals of treatment when confronted with this disease: presumably, our common goals of PCNSL treatment include: to improve neurological deficits, to improve or maintain quality of life, to delay neurological progression, to prolong progression-free survival, to prolong overall survival, and eventually to achieve a cure.

Very few of these goals are achieved with WBRT in the current landscape of improved systemic therapy options for PCNSL. Historically, it had been recognized that PCNSL is less sensitive to irradiation than lymphomas elsewhere in the organism and might therefore potentially require higher doses to achieve local control. Accordingly, Radiation Therapy Oncology Group (RTOG) study 8315 explored whether treating the whole brain at 40 Gy and increasing the tumor dose to

60 Gy would result in improved outcome. In fact, median overall survival was only 11.6 months from the start of radiotherapy; 16 of 26 patients with post-treatment CT scans were considered to have a complete response, a finding commonly cited to demonstrate the efficacy of RT in that disease. Importantly, however, these 16 patients represent a highly selected population because patients who progressed during radiotherapy were not included here.¹

With the introduction of high-dose methotrexate into the first-line treatment of PCNSL, the survival outcome was greatly improved, establishing initial chemotherapy containing high-dose methotrexate as a new standard of care, superiority of which, e.g., over RT alone, was never formally demonstrated in a randomized clinical trial. However, it became also soon apparent that the encouraging activity of combined modality treatment came at a high price. There was a major risk of severe neurotoxicity in surviving patients with a dramatic increase of risk in the elderly.² The association of the administration of WBRT and delayed neurotoxicity defined by cognitive decline and characteristic changes on neuroimaging has been confirmed repeatedly ever since.^{3,4} Accordingly, the increasing awareness that the administration of WBRT was probably incompatible with long-term survival with adequate quality of life resulted in numerous approaches to treat PCNSL with systemic chemotherapy or combined systemic and intraventricular chemotherapy alone.⁵⁻⁹ Yet, although retrospective analysis had failed to support a role for WBRT in prolonging overall survival many years ago,¹⁰ clinical practice did not respond and WBRT continued to be used at many sites throughout the world, even in the first-line setting. Thus, it was stated that the formal demonstration that WBRT could be omitted from the first-line treatment of PCNSL without compromising overall survival required a randomized clinical trial. This major endeavor was eventually agreed upon with the formation of the German PCNSL Study Group in the late nineties and took

until 2009 to complete enrolment. Patients with histologically confirmed PCNSL were to receive initial high-dose methotrexate chemotherapy, as monotherapy until 2005 and in combination with ifosfamide thereafter, as initial treatment. Patients who achieved a complete response were then treated with consolidating WBRT or observation alone, based on a randomization done prior to induction chemotherapy. Patients without a complete response were to be treated per initial randomization with WBRT or high-dose cytarabine. The latter was considered the best alternative systemic treatment at the time the trial was designed. The initial report of the primary outcome measures¹¹ as well as the final report¹² indicate that the omission of WBRT from the initial treatment does not compromise survival whichever way the data are explored, including various subgroup analyses.

Given the current dichotomy of PCNSL treatment of aiming for cure in young (fit) patients as opposed to maintaining remission in old (frail) patients,¹³ it becomes apparent that there is indeed no more role for WBRT in the initial treatment of the disease. If we want to cure young patients we cannot take the risk of inducing cognitive impairment for their remaining lifetime. In the elderly where we aim for maintaining the remissions we achieve, we should not use WBRT because of the strongly increased sensitivity of elderly patients to treatment-associated neurotoxicity. In light of the absence of a survival benefit for standard dose radiotherapy (30 x 1,5 Gy) in the G-PCNSL-SG-1 trial,^{11,12} the rationale of using a lower dose of WBRT, e.g. 13 x 1.8 Gy,¹⁴ in this setting remains doubtful.

This leaves us with the consideration of whether PCNSL should be treated with WBRT at recurrence. A retrospective study of 48 patients treated with salvage WBRT reported a complete response rate of 58% and a partial response rate of 21%, and median survival from initiation of WBRT was 16 months.¹⁵ While these data may be cited to support the role of WBRT in recurrent PCNSL, randomized data are again

more compelling and are in fact available looking into the G-PCNSL-SG1 trial.

Activity of WBRT as a salvage treatment was demonstrated for progression-free survival, but even here not for overall survival,¹¹ and the quality of post-progression survival with *versus* without WBRT remains to be explored.

Overall, these data available in the public domain allow to formulate some hypotheses on the treatment of PCNSL as summarized in the Table, and I would be hesitant to randomize either young or fit patients, or elderly or unfit patients, for a trial containing WBRT at any dose.

Is there no role for RT in this disease at all? Only prospective trials can support the claim that WBRT with hippocampal sparing is safer than standard WBRT, and this would only address the safety concern, not the efficacy concern. Could there be a role for focused RT e.g. in partial responders or to consolidate remission? Traditional views say “no”, but traditional views also said that there was no role for surgery until it was looked at in a reasonably sized patient population for the first time.¹⁶

References

1. Nelson DF, Martz KL, Bonner H, et al. Non-Hodgkin's lymphoma of the brain: can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315. *Int J Radiat Oncol Biol Phys.* 1992; 23: 9-17.
2. Abrey LE, DeAngelis LM, Yahalom J. Long-term survival in primary CNS lymphoma. *J Clin Oncol.* 1998; 16: 859-863.
3. Correa DD, Shi W, Abrey LE, et al. Cognitive functions in primary CNS lymphoma after single or combined modality regimens. *Neuro-Oncology.* 2012; 14: 101-8.

4. Doolittle ND, Korfel A, Lubow MA, et al. Long-term cognitive function, neuroimaging, and quality of life in primary CNS lymphoma. *Neurology*. 2013; 81: 84-92.
5. Batchelor T, Carson K, O'Neill A, et al. Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: a report of NABTT 96-07. *J Clin Oncol*. 2003; 21: 1044–1049.
6. Herrlinger U, Küker W, Uhl M, et al. NOA-03 trial of high-dose methotrexate in primary central nervous system lymphoma: final report. *Ann Neurol*. 2005; 57: 843–847.
7. Hoang-Xuan K, Taillandier L, Chinot O, et al. Chemotherapy alone as initial treatment for primary CNS lymphoma in patients older than 60 years: a multicenter phase II study (26952) of the European Organization for Research and Treatment of Cancer Brain Tumor Group. *J Clin Oncol*. 2003; 21: 2726–2731.
8. Pels H, Schmidt-Wolf IG, Glasmacher A, et al. Primary central nervous system lymphoma: results of a pilot and phase II study of systemic and intraventricular chemotherapy with deferred radiotherapy. *J Clin Oncol*. 2003; 21: 4489–4495.
9. Rubenstein JL, Hsi ED, Johnson JL, et al. Intensive chemotherapy and immunotherapy in patients with newly diagnosed primary CNS lymphoma: CALGB 50202 (Alliance 50202). *J Clin Oncol*. 2013; 31: 3061-3068.
10. Reni M, Ferreri AJ, Guha-Thakurta N, et al. Clinical relevance of consolidation radiotherapy and other main therapeutic issues in primary central nervous system lymphomas treated with upfront high-dose methotrexate. *Int J Radiat Oncol Biol Phys*. 2001; 51: 419-425.

11. Thiel E, Korfel A, Martus P, et al. G-PCNSL-SG-1 randomised phase III trial of high-dose methotrexate with or without whole brain radiotherapy for primary central nervous system lymphoma. *Lancet Oncol.* 2010; 11: 1036-1047.
12. Korfel A, Thiel E, Martus P, et al. G-PCNSL-SG-1 randomised phase III trial of high-dose methotrexate with or without whole brain radiotherapy for primary central nervous system lymphoma: long-term follow-up. *ASCO Proceedings.* 2014.
13. Roth P, Martus P, Kiewe P, et al. Outcome of elderly patients with primary CNS lymphoma in the G-PCNSL-SG-1 trial. *Neurology.* 2012; 79: 890-896.
14. Shah GD, Yahalom J, Correa DD, et al. Combined immunochemotherapy with reduced whole-brain radiotherapy for newly diagnosed primary CNS lymphoma. *J Clin Oncol.* 2007; 25: 4730–4735.
15. Hottinger AF, DeAngelis LM, Yahalom J, Abrey LE. Salvage whole brain radiotherapy for recurrent or refractory primary CNS lymphoma. *Neurology.* 2007; 69: 1178-1182.
16. Weller M, Martus P, Roth P, et al., for the German PCNSL Study Group. Surgery for primary CNS lymphoma? Challenging a paradigm. *Neuro-Oncology.* 2012; 14: 1481-1484.

Table. Key conclusions

- There is no safe dose of WBRT for the brain
- Reduced dose WBRT will not be more effective than standard dose WBRT
- Intensifying chemotherapy up-front will not make WBRT for consolidation more effective
- Intensifying chemotherapy up-front will not make WBRT for consolidation safer

- PCNSL needs to be „cured“ up-front, not at recurrence: WBRT at recurrence remains an option, but probably does not prolong survival