

Improving patient selection and outcome of stereotactic radiosurgery as a single treatment modality for brain metastases

Citation for published version (APA):

Zindler, J. D. (2017). *Improving patient selection and outcome of stereotactic radiosurgery as a single treatment modality for brain metastases*. [Doctoral Thesis, Maastricht University]. Datawyse / Universitaire Pers Maastricht. <https://doi.org/10.26481/dis.20171025jz>

Document status and date:

Published: 01/01/2017

DOI:

[10.26481/dis.20171025jz](https://doi.org/10.26481/dis.20171025jz)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Valorisation

Every year, approximately 75.000 cancer patients in the Netherlands develop brain metastases (BM).[1] Treatment for BM may have considerable impact on the national health care budget because of the number of patients affected. Traditionally, whole brain radiotherapy (WBRT) was the cornerstone of the treatment. Stereotactic radiosurgery (SRS) became available as an alternative for WBRT for patients with a limited number of brain metastases.[2] With SRS, several side effects of WBRT may be avoided, such as hair loss, fatigue, and neurocognitive damage.[3] In the Netherlands, the costs of WBRT are depend on contracts between the treating hospital and the insurance company and may differ per center. The content of these contracts is confidential. A crude estimation is that the costs of WBRT are around 4000 to 6000 euros and for SRS treatment around 6000 to 8000 euros. For patients with BM, SRS is more cost-effective than WBRT for patients with a limited life expectancy by the avoidance of costs related to neurocognitive side effects despite initial higher treatment costs as was published in American studies.[4,5] The exact cost-effectivity of SRS compared to WBRT or WBRT combined with SRS should also be studied specifically for the situation in the Netherlands.

The development of accurate prognostic models and shared decision tools allows individualized patient information per treatment modality. This may diminish the problem of over-treatment and intensive follow-up schemes for poor prognosis patients with BM. If patients are informed that there is a significant risk of dying within 3 months after treatment despite SRS, they may instead choose best supportive care.[6] Patients who have a low probability of long-term survival may choose not to undergo aggressive extracranial treatments, such as a 5 week treatment of chemotherapy and radiotherapy on the primary extracranial tumor with its morbidity and mortality. Patients who have only a low risk of developing distant brain recurrences (DBR) may choose not to undergo follow-up MRIs. All these choices may result in less treatment and imaging during follow-up of patients with BM and a reduction in the costs of their treatment.

Another opportunity to optimize cost-effectiveness is the potential avoidance of systemic therapies for patients with BM. For example, in a large trial in patients with a maximum of 3 BM of non-small cell lung cancer, RT only (WBRT + SRS) resulted in improved survival compared to combining RT with erlotinib or combining RT with temozolomide.[7] This can be explained by additional side effects caused by combining RT with relatively ineffective systemic agents, which may result in decreased general health condition and thereby survival. Because the RT-only arm resulted in the best survival, it is obvious that both trial arms with the combination treatments (RT + erlotinib or RT + temozolomide) are less cost-effective by additional costs of the systemic agents with even a detrimental effect on survival compared to RT only. One year of treatment with a daily dose of 150 mg erlotinib costs 28.568 Euros in the Netherlands. One year of treatment with a daily dose of 100 mg temozolomide costs 6732 Euros in the Netherlands (www.medicijnkosten.nl). Thus, combining systemic agents with RT will only be

cost-effective if survival is actually improved over RT only and additional side effects of combining treatments are absent.

Another opportunity to optimize cost-effectiveness is the application of isotoxic dose prescription (IDP). With IDP, the risk of radionecrosis (RN) is low because the SRS dose is prescribed based on normal tissue tolerance levels. With standard risk-adapted SRS dose prescription in large BM, there is a relatively low risk of local control and a relatively high risk of RN.[8] Application of IDP in large inoperable BM (for example, PTV > 10 cm³) is expected to result in a lowering of the incidence of RN compared to the current daily clinical practice. Patients suffering from RN become often dependent on steroids. Steroids have significant side effects such as a risk of diabetes mellitus with a need for medication, myopathy with a need for adaptations at home in daily care, and sleepiness with a need for medications. Symptoms resulting from RN and side effects resulting from steroids may also increase health care costs. It is to be expected that the application of IDP in daily clinical practice with SRS for BM will result in a reduction in costs due to a lower incidence of RN and simultaneously an increase in cost-effectivity by higher local control probability in large BM.

REFERENCES

- [1] www.kankerregistratie.nl
- [2] Zindler JD, Rodrigues G, Haasbeek CJ, Haan PF, Meijer OW, Slotman BJ, Lagerwaard FJ. The clinical utility of prognostic scoring systems in patients with brain metastases treated with radiosurgery. *Radiother Oncol* 2013 Mar;106(3):370-4.
- [3] Soffiotti R, Kocher M, Abacioglu UM, Villa S, Fauchon F, Baumert BG, Fariselli L, Tzuk-Shina T, Kortmann RD, Carrie C, Ben Hassel M, Kouri M, Valeinis E, van den Berge D, Mueller RP, Tridello G, Collette L, Bottomley A. A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. *J Clin Oncol*. 2013 Jan 1;31(1):65-72.
- [4] Hall MD, McGee JL, McGee MC, Hall KA, Neils DM, Klopfenstein JD, Elwood PW. Cost-effectiveness of stereotactic radiosurgery with and without whole-brain radiotherapy for the treatment of newly diagnosed brain metastases. *J Neurosurg*. 2014 Dec;121 Suppl:84-90.
- [5] Lester-Coll NH, Dosoretz AP, Magnuson WJ, Laurans MS, Chiang VL3, Yu JB. Cost-effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for up to 10 brain metastases. *J Neurosurg*. 2016 Dec;125(Suppl 1):18-25.
- [6] Zindler JD, Jochems A, Lagerwaard FJ, Beumer R, Troost EG, Eekers DB, Compter I, Van der Toorn PP, Essers M, Oei B, Hurkmans CW, Bruynzeel AM, Bosmans G, Swinnen A, Leijenaar RT; Lambin P. Individualized early death and long-term survival prediction after stereotactic radiosurgery for brain metastases of non-small cell lung cancer: two externally validated nomograms - submitted
- [7] Sperduto PW, Wang M, Robins HI, Schell MC, Werner-Wasik M, Komaki R, Souhami L, Buyyounouski MK, Khuntia D, Demas W, Shah SA, Nedzi LA, Perry G, Suh JH, Mehta MP. A phase 3 trial of whole brain radiation therapy and stereotactic radiosurgery alone versus WBRT and SRS with temozolomide or erlotinib for non-small cell lung cancer and 1 to 3 brain metastases: Radiation Therapy Oncology Group 0320. *Int J Radiat Oncol Biol Phys*. 2013 Apr 1;85(5):1312-8.
- [8] Zindler JD, Schiffelers J, Lambin P, Hoffmann A. Individualized isotoxic dose prescription for stereotactic radiotherapy in large brain metastases: an in-silico study – submitted.