REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY 18 (2013) 133–138

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: http://www.elsevier.com/locate/rpor

Review

Whole brain radiotherapy: Consequences for personalized medicine

Tomáš Kazda[a,*], *Petr Pospíšil*[a], *Hana Doleželová*[a], *Radim Jančálek*[b], *Pavel Šlampa*[a]

[a] *Department of Radiation Oncology, Faculty of Medicine, Masaryk University and Masaryk Memorial Cancer Institute, Žlutý kopec 7, Brno 656 53, Czech Republic*

[b] *International Clinical Research Center – Department of Neurosurgery, St. Anne's University Hospital Brno, Brno, Czech Republic*

ARTICLE INFO

Article history:
Received 4 October 2012
Received in revised form
7 January 2013
Accepted 17 March 2013

Keywords:
Whole brain radiotherapy
Brain metastases
Decision-making
Personalized medicine

ABSTRACT

Several studies focusing on brain irradiation are in progress. Reflecting updates of relevant outcomes in palliative treatment of patients suffering from brain metastases, the primary objective of these studies is the evaluation of neurocognitive function and quality of life. Improvements of technology in radiation oncology allows us to spare the hippocampal region while appropriately irradiating other parts of brain tissue. Irradiation of the hippocampus region is likely to lead to manifestations of adverse events with a subsequent impact on patient's quality of life, which is in fact an improper approach in palliative medicine. Ongoing studies evaluate results of hippocampus avoiding radiotherapy compared to standard whole brain radiotherapy. Incorporation of neurocognitive function assessment may result in the confirmation of superiority of sparing the region of hippocampus and thus change current style of providing brain irradiation.

1. Background

Approximately 30% of patients develop brain metastases (BM) as a part of their cancer disease.[1] This number is expected to grow due to an increasing number of registered preparations from targeted therapy drugs, improvement of surgical and radiotherapy methods and an increased availability of better palliative and supportive care. Increasing incidence of BM is also due to improvements in imaging technologies and their higher availability.[2] Brain metastases are considered to be one of the most serious complications of cancer disease, which dramatically increase the morbidity and mortality. Their optimal treatment remains controversial, mainly with respect to the aim of provided medical care.[3] In most cases of patients with metastases (MTS) of any location, the treatment aim is not to destroy all cancer cells and cure the patient, but to reduce actual difficulties and prolong the overall survival with good quality of remaining life by achieving an appropriate reduction of symptoms and prevention of its further

* *Corresponding author.* Tel.: +420 543 131 187; fax: +420 543 131 179.
E-mail addresses: tomas.kazda@mou.cz (T. Kazda), ppospisil@mou.cz (P. Pospíšil), dolezelova@mou.cz (H. Doleželová), radim.jancalek@fnusa.cz (R. Jančálek), slampa@mou.cz (P. Šlampa).

1507-1367/$ – see front matter
http://dx.doi.org/10.1016/j.rpor.2013.03.002

impairment.[4] Besides the reduction of symptoms, the goal of a good palliation is to minimize its side effects. In order to achieve this aim, it is important to determine appropriate end-points not only in relation to an individual patient, but also in relation to the ongoing randomized clinical trials (RCT) as resources for future treatment guidelines. Recently, more attention has been paid to symptom-related outcomes of care, especially to neurocognitive functions (NCF) and quality of life as the most frequently mentioned issues.[5]

One of the standard therapeutic methods of brain metastases is radiotherapy (RT), which offers several possibilities to influence further progression of disease. Apart from the basic technique, i.e. radiation of the whole brain (WBRT – whole brain radiotherapy), new treatment methods are being put into practice, such as stereotactic methods of intracranial radiosurgery or radiotherapy. These novel methods allow delivering higher doses of radiation into a small amount of tissue. However, these techniques remain available only for a small group of patients.[6] Recently, a lot of trials have been conducted to compare different radiotherapy techniques as separate methods of treatment to their combinations. Other studies deal with a combination of radiotherapy and neurosurgery.

In most patients the radiation of the whole brain is indicated because of numerous brain metastases present or because of unmanageable extracranial illness. Thus, attention must also be paid to the development of further improvements in providing WBRT, especially in the light of new knowledge about radiation brain injury mechanisms and in respect to the personalized palliative approach to each patient. In this article, we focus mainly on the whole brain radiotherapy.

In general, one of the main future directions in the treatment of cancer patients is the implementation of so called tailor-made personalized medicine into clinical practice. That means optimization of drug prescription based on patient's individual gene profile in a narrower sense. Although this concept applies particularly to systemic treatment with chemotherapeutic agents, some principles of this philosophy could be implemented into other areas of care for cancer patients, meaning the pursuit of individualized approach to the treatment. One of the basic principles of tailor-made personalized medicine is the usage of a specific procedure for the specific patient, in order to maximize, if possible, the therapeutic effect while avoiding side effects.

In relation to the facts mentioned above, it is necessary to take into account some patient-specific variables while making decisions about indications to cranial irradiation. At first, the question is if patient can realistically benefit from being provided such irradiation. In practice it is about responsible life expectancy estimation (for example expressed by the Karnofsky Performance Scale) and about considering all consequences relating to the actual possibilities to provide the care. If RT is indicated, the next question is what part of brain should be irradiated and how. Choosing the right procedure is important in relation to the assessment of all benefits and risks of our intervention. We summarize some recent recommendations in the use of WBRT and mention some future directions related to this issue.

2. Indications for WBRT

In daily radiotherapy practice, one of the most important factors in decision-making is the level of technical equipment in a particular radiotherapy department. Not all departments are able to provide their patients with the most advanced care, e.g. precise stereotactic radiosurgery (SRS), or WBRT with simultaneous integrated boost (SIB) to BM using volumetric modulated arc therapy delivered by helical tomotherapy or by linear accelerators (Rapid Arc, IMAT/VMAT therapy).[7] Thus, also because of this technical limitation, WBRT remains the most commonly radiotherapy method used in the treatment of patients with brain metastases.

When considering the best specific type of treatment it is important to compare all its pros and cons. In general, palliative treatment should be as undemanding as possible in order not to burden patients with long complex treatment. Cost of this care should be low or at least weighed against potential benefits in comparison with other lower or more expensive alternatives.[3]

Before starting treatment it is useful to recognize the number of BM – single lesion, oligometastatic (2–3) or multiple impairments. It is also very important to properly assess the general performance status and consider other specific clinical situations (presence or absence of extracranial metastases). These are the most common prognostic/predictive factors mentioned in recent guidelines. Karnofsky Performance Scale (KPS) is the most useful tool to estimate patient's ability to profit from any kind of treatment. Indeed, KPS is a part of all tools for stratification of patients into prognostic groups – Recursive Partitioning Analysis and Graded Prognostic Index (RPA and GPI score).[8,9] Patients with KPS of less than 70% (RPA group III) will benefit from WBRT compared to other type of brain radiotherapy regardless of the type of brain impairment.

Several studies have been performed to assess the importance of the implementation WBRT in combination with local treatment of brain metastases.[10–13] Abe et al.[14] reviewed these findings and concluded, that initial local brain radiotherapy without its whole irradiation does not influence overall survival, but results in a significant increase in brain tumor recurrence (BTR), while the inclusion of WBRT into the primary treatment prolongs time to recurrence and prevents neurologic death.[14]

Brain tumor recurrence means the clinical progression resulting in severe impact on patient's quality of life. BTR is the most important cause of additional deterioration of NCF. It seems that it is useful to stratify patients into the low and high risk group of BTR and hence determine the indication for WBRT.[11] Aoyama also evaluated the risk of developing brain metastases in breast cancer patients after up-front WBRT according to the risk of BTR. Patients in high BTR risk group (2 or more BM, presence of extracranial metastases) who underwent WBRT developed BTR in other site of brain in 21% at 6 months compared to 57% of patients without WBRT. Patients in the low BTR risk group (single BM, no extracranial metastases) with and without WBRT developed BTR at 6 months in 9%, vs. 31%, respectively.[15]

WBRT as a separate up-front treatment is a possible option for all prognostic groups in both most common scoring systems – RPA and GPA. That means that the choice of the type of radiotherapy offered to patients of the low risk group depends mostly on the technical equipment of the radiotherapy department. Patients with poor prognostic factors (RPA III group) benefit from WBRT alone the most.

3. Performing WBRT

In general, one of the most important outcomes in RCT is overall survival. Considering that most of patients presented with brain metastases die because of the progression of their extracranial disease, the overall survival seems not to be the best factor to assess during decision making for management of brain metastases. It is more important to consider the aim of our treatment and that is, as obvious in the palliative approach, symptoms relief, attempt to improve the overall survival while maintaining appropriate quality of life, in accordance with the general principle of "primum non nocere". This means maintaining good mental conditions, too. More recently, endpoints in brain tumor clinical trials have been refined, with emphasis put on the neurocognitive assessment and evaluation of the quality of life.[5,16]

Results of studies comparing different radiotherapy techniques report some changes in cognitive functions due to radiation.[17] The most serious cause of its alteration is a recurrence of cancer disease in brain; its risk might be assessed by BTR as mentioned above.[18] The risk of relapse is, however, smaller if aggressive therapy for brain metastases is used. It is essential to find a compromise between the benefits of such aggressive treatment in the sense of reducing the risk of later intracranial progression versus higher risk of iatrogenic alteration of cognitive functions and thus decrease in the quality of life, which is a very important endpoint for a good palliation. The impact of WBRT on reducing incidence of brain tumors relapse has been demonstrated in several RCTs. The omission of WBRT results in a relative increase of a BTR from 70% to 300% (calculated in the original article from absolute BTR risk with and without WBRT, which was 18% and 70%, respectively).[19]

Li et al.[20] confirmed that there is a correlation between tumor regression after WBRT and the improvement of some types of NCF. In contrast, memory-related NCF had a lower correlation with rated reduction of MTS deposits, suggesting different mechanisms of alteration of different kinds of NCF by cranial irradiation.[20] Nevertheless, it is clear, that WBRT plays an important role in protecting patients from decline in some types of NCF.

In fact, the development of brain metastases is based on hematogenous dissemination from primary or other sites. Impairment probability of certain parts of the brain depends also on its perfusion. 80% of all brain blood supply is deposited in the telencephalon, so it is the most frequently affected part.[21] But it is true that the whole brain can be seeded by BM, therefore, WBRT seems to be the best approach to control brain metastases.

The standard technique of WBRT involves the use of two opposed contralateral radiation fields with homogenous irradiation of the whole brain.[22] Shielding the eyes and other parts of splanchnocranium is performed using multileaf collimator at most. This technique requires only a simple planning with minimal personal and technical burden. The whole process of radiotherapy can be planned on the 2D X-ray simulator, so it is available also in the absence of the CT simulator. In this setting of WBRT, the whole brain is homogenously irradiated. The radiation dose is the same in areas of proven MTS as it is in areas without apparent MTS. However, it remains uncertain whether it is important to irradiate all parts of the brain, especially the region of the hippocampus. Provided that the hippocampus is unimpaired, it seems that benefits of its irradiation do not outweigh the potential risk of radiation injury. Alteration in the processes of learning or spatial memory processing is related to hippocampal injury.[23] The relationship between hippocampal radiation injury and alteration of NCF has been demonstrated also by Monje et al.[24,25] It is estimated, that only 3% of all BM are located in perihippocampal parts of the brain (within 5 mm of the hippocampus)[26]. New methods of WBRT have been developed in order to minimize the side effects resulting from irradiation of the hippocampal region.

4. Future directions

With a development of other therapeutic methods and with an increase in effectiveness of supportive and symptomatic treatment, the prolongation of overall survival in certain groups of patients is achieved after WBRT. These are mainly patients suffering from breast cancer.[27] We may expect the manifestation of long-term side effects of radiation to develop in these patients, including at most, the impairment of cognitive functions. Some degree of cognitive function alteration can be observed at baseline, due to the primary status of cancer disease and other factors.[28] In recent years, there has been a discussion on the significance of damage of neuronal stem cells due to ionizing radiation, with impact on changes of cognitive functions.[29] Neuronal stem cells are located in the hippocampal subgranular zone of the dentate gyrus. Their significance in relation to the process of learning and memory recall has been demonstrated in many studies.[30,31]

Nowadays, randomized clinical trials comparing the therapeutic results using different radiotherapy techniques are in progress, where the hippocampus region is protected in certain groups of patients.[32] Protecting of the hippocampus is ensured by using intensity modulated radiotherapy enabling high conformal radiotherapy with a steep dose gradient in locations with high priority of sparing. Providing this modern therapy places high demands on the accuracy of radiation and precision of planning. Despite RT techniques, the use of simple planning, as described above, is being developed.[33] The avoidance of the hippocampus in WBRT with evaluation memory delayed recall as a primary objective is a subject of ongoing prospective RTOG study (RTOG 0933).[34] Key studies and reviews reflecting preclinical and clinical evidence supporting performance of hippocampus-avoiding whole brain radiotherapy are summarized in Table 1.

The growing interest in optimizing care of patients with brain metastases is also reflected in the growing number of

Table 1 – Key studies and reviews demonstrating preclinical and clinical evidence supporting performing of hippocampus-avoiding whole brain radiotherapy.

Author	Year	Conclusion	Consequences
Abe[14]	2012	Omission of WBRT results in increasing of BTR	WBRT is still an important part of RT management of brain metastases. Importance of selective indications for local treatment only
Meyers[5]	2012	Quality of life optimization of brain tumor patients is essential while prolongation of overall survival is achieved	Emphasis on the neurocognitive assessment and evaluation of quality of life in ongoing trials
Bayer[35] and Eriksson[30]	1982 and 1998	New granule cells are generated from neuronal stem cells located in the dentate gyrus	Neuronal stem cells hypothesis approved
Collier[36]	1987	Memory function are associated with dentate gyrus of the hippocampus	Hippocampal damage will result in memory function decline
Mizumatsu[25]	2003	Pathogenesis of RT-induced NC deficit is in relation with NSC	CNS is not exclusively radio-resistant organ
Abayomi[23] and Jalali[37]	1996 and 2010	There is evidence in radiotherapy of brain and NC function impairment	Hippocampal sparing RT can reduce memory impairment after WBRT
Gondi[38]	2010	There is ability of modern RT techniques to spare region of hippocampus while delivering appropriate dose into the other parts of brain	Superiority of hippocampal - avoidance WBRT must be evaluated by a prospective clinical trial
Mehta[34], RTOG 0993 study	2012	A Phase II Trial of Hippocampal Avoidance During Whole Brain Radiotherapy for Brain Metastases	Prospectively evaluation of the NC benefit of hippocampal sparing during RT

WBRT, whole brain radiotherapy; BTR, brain tumor recurrence; RT, radiotherapy; NC, neurocognitive; NSC, neuronal stem cells; CNS, central nervous system.

studies and articles dealing with this subject. As showed in Fig. 1, there is a clear growth in publishing review articles on WBRT linked at MEDLINE PubMed. Current year's results are interpolated to 12 months to allow comparison with other years. Discussing of NCF is their part mainly at last 6 years. Standardized regular assessment of neurocognitive functions in patients with radiotherapy of brain is an essential step forward to implementation of modern radiotherapy methods into clinical practice.

If ongoing studies confirm that patients undergoing hippocampus-avoiding WBRT do not have increased risk of brain tumor recurrence while better preserving the neurocognitive function as a result of radiation to brain injury, providing hippocampus sparing radiotherapy will become the new method of choice. Then, it will be necessary to correctly estimate the risk of development of brain metastases in the perihippocampal region and to incorporate this factor into upgraded scoring systems.

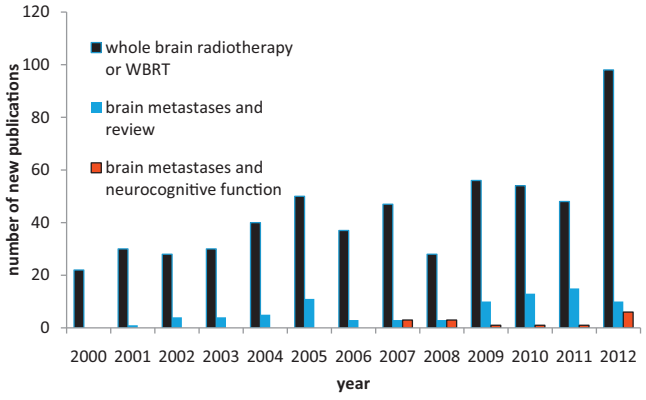

Fig. 1 – Number of new publications in PubMed database when entering given keywords as mentioned in graph.

It might be assumed that the withholding of WBRT will not be the subject of further research. As suggested in several studies (mentioned above) comparing the local treatment of brain metastases with WBRT, WBRT leads to a significant reduction in the risk of brain tumor recurrence and in the risk of neurological death. While providing the hippocampal sparing brain irradiation using modern radiotherapy techniques, it is also possible to increase the dose of radiation to areas of proven metastases (SIB). Combining these two approaches in a particular patient case, may improve the efficacy of radiation therapy while reducing the risk of late side effects. This means an individualized care as a type of personalized medicine in a wider sense.

Taking into account an increasing number of patients with brain metastases, studies dealing with this subject are becoming an important direction of further radiotherapy research. There is also an increasing number of diagnoses of early asymptomatic BM, because of examination of patients in relation to their enrollment into some clinical trials, where MRI of brain is performed as one of inclusion criteria. In these cases, a decision making is influenced by the consideration of specific trial enrollment criteria and by the fact, that these patients are often long survivals.

5. Summary

Several studies focusing on brain irradiation are in progress. Reflecting updates of relevant outcomes in palliative treatment of patients suffering from brain metastases, the primary

objective of these studies is the evaluation of neurocognitive function and quality of life. Improvements of technology in radiation oncology allows us to spare the hippocampal region while appropriately irradiating other parts of brain tissue. Irradiation of the hippocampus region is likely to lead to manifestations of adverse events with a subsequent impact on patient's quality of life, which is in fact an improper approach in palliative medicine. Ongoing studies evaluate results of hippocampus avoiding radiotherapy compared to standard whole brain radiotherapy. Incorporation of neurocognitive function assessment may result in the confirmation of superiority of sparing the region of hippocampus and thus change current style of providing brain irradiation.

Conflicts of interest

None declared.

Acknowledgements

The work was supported by the European Regional Development Fund and the State Budget of the Czech Republic (RECAMO, CZ.1.05/2.1.00/03.0101).

This study was funded by Institutional Resources for Supporting the Research Organization provided by the Ministry of Health of the Czech Republic in 2012.

Supported by European Regional Development Fund – Project FNUSA-ICRC (No. CZ.1.05/1.1.00/02.0123).

Supported by MZCR IGA NT/14600.

Supported by MZCR IGA NT/14120.

REFERENCES

1. Wen PY, Black PM, Loeffler JS. Metastatic brain cancer. In: DeVita V, Hellman S, Rosenberg SA, editors. *Cancer: principles and practice of oncology*. Philadelphia, PA: Williams & Wilkins/Lippincott; 2001. p. 2655–70.
2. Seute T, Leffers P, ten Velde GP, Twijnstra A. Detection of brain metastases from small cell lung cancer: consequences of changing imaging techniques (CT versus MRI). *Cancer* 2008;**112**(8):1827–34.
3. Marc D, Okunieff P, Milano MT. Brain metastases. In: Gunderson LL, Tepper JE, editors. *Clinical radiation oncology*. Philadelphia: Elsevier Saunders; 2012. p. 421–38.
4. National Comprehensive Cancer Network (NCCN). *NCCN Clinical Practice Guidelines in Oncology. Palliative care Version 2.2012*; 2012. Online at http://www.nccn.org/professionals/physician_gls/pdf/palliative.pdf. Version 2 (last accessed 09.09.12).
5. Meyers CS, Rock EP, Fine HA. Refining endpoints in brain tumor clinical trials. *J Neurooncol* 2012;**108**(2):227–30.
6. Linskey ME, Andrews DA, Asher AL, et al. The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systemic review and evidence-based clinical practice guideline. *J Neurooncol* 2010;**96**:45–68.
7. Saminathan S, Chandraraj V, Sridhar CH, Manickam R. Comparison of individual and composite field analysis using array detector for intensity modulated radiotherapy dose verification. *Rep Pract Oncol Radiother* 2012;**17**(3):157–62.
8. Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three radiation therapy oncology group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys* 1997;**37**:745–51.
9. Sperduto PW, Berkey B, Gaspar LE, et al. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. *Int J Radiat Oncol Biol Phys* 2008;**70**:510–4.
10. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA* 1998;**280**:1485–9.
11. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA* 2006;**295**:2483–91.
12. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol* 2009;**10**:1037–44.
13. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol* 2011;**29**(2):134–41.
14. Abe E, Aoyama H. The role of whole brain radiation therapy for the management of brain metastases in the era of stereotactic radiosurgery. *Curr Oncol Rep* 2012 Feb;**14**(1):79–84.
15. Aoyama H. Radiation therapy for brain metastases in breast cancer patients. *Breast Cancer* 2011;**18**(4):244–51.
16. Fernandes G, Pocinho R, Travancinha C, Netto E, Roldao M. Quality of life and radiotherapy in brain metastasis patients. Rep Pract Oncol Radiother. Article available online at http://www.sciencedirect.com/science/article/pii/S1507136712001290 (05.09.12), http://dx.doi.org/10.1016/j.rpor.2012.08.003
17. Aoyama H, Tago M, Kato N, et al. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. *Int J Radiat Oncol Biol Phys* 2007;**68**:1388–95.
18. Scoccianti S, Ricardi U. Treatment of brain metastases: review of phase III randomized controlled trials. *Radiother Oncol* 2012;**102**:168–79.
19. Gondi V, Tomé Wa, Mehta MP. Why avoid the hippocampus? A comprehensive review. *Radiother Oncol* 2010;**97**(December (3)):370–6.
20. Li J, Bentzen SM, Renschler M, et al. Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function. *J Clin Oncol* 2007;**25**:1260–6.
21. Delattre JY, Krol G, Thaler HT, et al. Distribution of brain metastases. *Arch Neurol* 1988;**45**:741–4.
22. Barret A, Dobbs J, Morris S, Roques T. Cerebral metastases. In: Barret A, Dobbs J, Morris S, Roques T, editors. *Practical radiotherapy planning*. London: Hodder Arnold; 2009. p. 227–30.
23. Abayomi OK. Pathogenesis of irradiation-induced cognitive dysfunction. *Acta Oncol* 1996;**35**:659–63.
24. Monje ML, Mizumatsu S, Fike JR, et al. Irradiation induces neural precursor-cell dysfunction. *Nat Med* 2002;**8**:955–62.
25. Mizumatsu S, Monje ML, Morhardt DR, et al. Extreme sensitivity of adult neurogenesis to low doses of X-irradiation. *Cancer Res* 2003;**63**:4021–7.
26. Gondi V, Tome WA, Marsh J, et al. Estimated risk of perihippocampal disease progression after hippocampal avoidance during whole-brain radiotherapy: safety profile for RTOG 0933. *Radiother Oncol* 2010;**95**(3):327–31.
27. Palacova M, Svoboda M, Fabian P, et al. Tumor phenotype and characteristics of metastatic brain involment in breast cancer patients: potential clinical consequences, ASCO annual meeting proceedings 2009. *J Clin Oncol* 2009;**27**(15):1026.

28. Scoccianti S, Detti B, Cipressi S, et al. Changes in neurocognitive functioning and quality of life in adult patients with brain tumors treated with radiotherapy. *J Neurooncol* 2012;**108**:291–308.
29. Monje ML, Palmer T. Radiation injury and neurogenesis. *Curr Opin Neurol* 2003;**16**:129–34.
30. Eriksson PS, Perfilieva E, Bjork-Eriksson T, et al. Neurogenesis in the adult human hippocampus. *Nat Med* 1998;**4**:1313–7.
31. Gould E, Beylin A, Tanapat P, et al. Learning enhances adult neurogenesis in the hippocampal formation. *Nat Neurosci* 1999;**2**:260–5.
32. Marsh JC, Gielda BT, Herskovic AM, Abrams RA. Cognitive sparing during the administration of whole brain radiotherapy and prophylactic cranial irradiation: current concepts and approaches. *J Oncol* 2010:198–208.
33. van Kesteren Z, Belderbos J, van Herk M, et al. A practical technique to avoid the hippocampus in prophylactic cranial irradiation for lung cancer. *Radiother Oncol* 2012;**102**(February (2)):225–7.
34. Mehta MP. A phase II trial of hippocampal avoidance during whole brain radiotherapy for brain metastases. RTOG 0933 study protocol. Available online at http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0933 (last accessed 09.09.12).
35. Bayer SA. Changes in the total number of dentate granule cells in juvenile and adult rats: a correlated volumetric and 3H-thymidine autoradiographic study. *Exp Brain Res* 1982;**46**:315–23.
36. Collier TJ, Quirk GJ, Routtenberg A. Separable roles of hippocampal granule cells in forgetting and pyramidal cells in remembering spatial information. *Brain Res* 1987;**409**:316–28.
37. Jalali R, Mallick I, Dutta D, et al. Factors influencing neurocognitive outcomes in young patients with benign and low-grade brain tumors treated with stereotactic conformal radiotherapy. *Int J Radiat Oncol Biol Phys* 2010;**77**:974–9.
38. Gondi V, Tolakanahalli R, Mehta MP, et al. Hippocampal-sparing whole-brain radiotherapy: a "how-to" technique using helical tomotherapy and linear accelerator-based intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2010;**78**:1244–52.