Left hippocampus sparing whole brain radiotherapy (WBRT): A planning study

Tomas Kazda^{a,b}, Miroslav Vrzal^{a,b}, Tomas Prochazka^{a,b}, Petr Dvoracek^{a,b}, Petr Burkon^{a,b}, Petr Pospisil^{a,b}, Adam Dziacky^c,
Tomas Nikl^{a,b}, Radim Jancalek^{d,e}, Pavel Slampa^{a,b,h}, Radek Lakomy^{f,g}

Aims. Unilateral sparing of the dominant (left) hippocampus during whole brain radiotherapy (WBRT) could mitigate cognitive decline, especially verbal memory, similar to the widely investigated bilateral hippocampus avoidance (HA-WBRT). The aim of this planning study is dosimetrical comparison of HA-WBRT with only left hippocampus sparing (LHA-WBRT) plans.

Methods. HA-WBRT plans for 10 patients were prepared in accordance with RTOG 0933 trial and served as baseline for comparisons with several LHA-WBRT plans prepared with an effort: 1) to maintain the same left hippocampus dosimetry ("BEST PTV") and 2) to maintain same dosimetry in planning target volume as in HA-WBRT ("BEST LH").

Results. All HA-WBRT plans met RTOG 0933 protocol criteria with a mean Conformity index 1.09 and mean Homogeneity index (HI) 0.21. Mean right and left hippocampal D100% was 7.8 Gy and 8.5 Gy and mean Dmax 14.0 Gy and 13.8 Gy, respectively. "BEST PTV" plans reduced HI by 31.2% ($P=0.005$) which is mirrored by lower PTV_D2% (-0.8 Gy, $P=0.005$) and higher PTV_D98% (+1.3 Gy, $P=0.005$) as well as decreased optic pathway's Dmax by 1 Gy. In "BEST LH", mean D100% and Dmax for the left hippocampus were significantly reduced by 11.2% ($P=0.005$) and 10.9% ($P=0.005$) respectively.

Conclusions. LHA-WBRT could improve target coverage and/or further decrease in dose to spared hippocampus. Future clinical trials must confirm whether statistically significant reduction in left hippocampal dose is also clinically significant.

Key words: brain metastases, hippocampus, memory, cognition, HA WBRT

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^aDepartment of Radiation Oncology, Faculty of Medicine, Masaryk University, Kamenice 5, 625 00 Brno, Czech Republic

^bDepartment of Radiation Oncology, Masaryk Memorial Cancer Institute, Zluty kopec 7, 656 53 Brno, Czech Republic

^cFaculty of Medicine, Masaryk University, Kamenice 5, 625 00 Brno, Czech Republic

^dDepartment of Neurosurgery, St. Anne's University Hospital Brno and Faculty of Medicine, Masaryk University, Kamenice 5, 625 00 Brno, Czech Republic

^eDepartment of Neurosurgery, St. Anne's University Hospital Brno, Pekarska 53, 656 91 Brno, Czech Republic

^fDepartment of Comprehensive Cancer Care, Faculty of Medicine, Masaryk University, Kamenice 5, 625 00 Brno, Czech Republic

^gDepartment of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute, Zluty kopec 7, 656 53 Brno, Czech Republic

^hRegional Center for Applied Molecular Oncology (RECAMO), Masaryk Memorial Cancer Institute, Zluty kopec 7, 656 53 Brno, Czech Republic
Corresponding author: Radek Lakomy, e-mail: lakomy@mou.cz

INTRODUCTION

Hippocampal sparing during whole brain radiotherapy (WBRT) in an effort to preserve cognitive function is a currently widely investigated approach in palliative irradiation in patients with brain metastases unsuitable for local treatment¹. Many planning studies have shown the dosimetric feasibility of hippocampus avoiding (HA) WBRT in different clinical situations using many different radiotherapy systems and techniques²⁻⁵. However, these studies must be considered as experimental until well designed clinical trials with appropriate endpoints definitely reveal the significant clinical benefit of these novel approaches^{2,6}. Further, some reports suggest different post radiotherapy and/or post surgery changes in the two hippocampi. As a result, unilateral hippocampal sparing has been proposed⁷⁻¹¹.

The most important neurocognitive domain affected by WBRT is memory. Radio-injury of the left, usually dominant, hippocampus may affect the formation of memory to a greater extent, in particular verbal

memory^{9,11}. Dosimetric consequences of potential unilateral (left) hippocampus sparing during WBRT are not known. We hypothesize that left hippocampal avoiding (LHA) during WBRT can possibly reduce the dose within the spared hippocampus as well as improve dose coverage of the remaining brain including the right hippocampus. Minimizing the dose to the least possible level is of high clinical relevance since higher hippocampal D_{100%} was shown to predict greater decline in some memory tests over time^{12,13}. Also, the dose-response relationship between equivalent dose in 2-Gy fractions to 40% of the bilateral hippocampi (EQD_{2Gy} 40%) and impairment in delayed recall at 18 months was described after fractionated stereotactic radiotherapy for benign or low-grade brain tumors¹². The aim of this planning study was to compare HA-WBRT with LHA-WBRT treatment plans, paying particular attention to left hippocampal dosimetry and quantitatively describe the potential benefit of only one-sided hippocampal sparing. To the best of our knowledge, this is the first report of the practical consequences of LHA-WBRT.

MATERIALS AND METHODS

Patients and contouring

This retrospective planning study included ten consecutive patients with brain metastases and with available planning CT and MRI scans (9 women, mean age 54 years, 5/10 with lung cancer). Left and right hippocampi were separately contoured using the free available online RTOG contouring atlas as a reference¹⁴. A five millimeter margin around each hippocampus was created for the planning at risk volume (PRV) (ref.¹⁵). Other organs at risk (optic nerves, chiasm and lenses) were segmented according to recent contouring guidelines¹⁶. Planning target volume (PTV) contained the whole brain with 5 mm expansion to accommodate random setup uncertainty.

Three different treatment plans were created for each patient as described below (Fig. 1):

- 1) "standard" HA-WBRT serving as the baseline plan,
- 2) LHA-WBRT maintaining the same left hippocampal dosimetry as in the baseline plan (labeled as "BEST PTV") and
- 3) LHA-WBRT maintaining the same baseline plan's PTV's dosimetry (labeled as "BEST LH").

For "standard" HA-WBRT, both hippocampi_PRV were cropped out, while only the left hippocampus_PRV was cropped out for LHA-WBRT plans. Thus, these experimental plans included the entire right hippocampus within PTV.

Experimental treatment plans

All treatment plans were created utilizing EclipseTM treatment planning system (Varian Medical Systems, Palo Alto, CA). The dose calculation was performed using the Anisotropic Analytical Algorithm (v11, Varian Medical Systems, Palo Alto, CA) with a 2.5 mm grid size and with the heterogeneity correction turned on. VMAT treatment plans were created for a TrueBeam STX with HD120 MLC (2.5 mm leaf width at isocenter). The 6 MV photon beam model were used in all plans. The CT images which were used for planning were 3 mm slices.

Baseline plans for bilateral hippocampus sparing WBRT were created in accordance with online available RTOG 0933 (phase II trial assessing bilateral HA WBRT) study protocol criteria as follows: 90 % of PTV receiving 10 x 3 Gy; $PTV_D_{2\%} \leq 37.5$ Gy, $PTV_D_{98\%} \geq 25$ Gy; D_{max} of optic nerves or optic chiasm ≤ 37.5 Gy, Hippocampal $D_{100\%} \leq 9$ Gy and Hippocampal $D_{max} \leq 16$ Gy (ref.^{13,15}). $D_{x\%}$ represents the dose received by x % of specified structure. All treatment plans utilized three coplanar full arcs and one non-coplanar semi arc (couch angle 90 degrees and partial non-coplanar arc spanning 194 degrees (from 345 to 179 degrees)) in order to meet planning constraints criteria as much as possible.

Dosimetric analysis

The following parameters were reported for PTV: $V_{100\%}$, $PTV_D_{2\%}$, $PTV_D_{98\%}$, conformity index (CI) and homogeneity index (HI). CI was calculated based on the formula: $(V_{95\%Rx}/V_{PTV})$, where $V_{95\%Rx}$ is the volume encompassed by 95% of the prescription isodose surface. This definition of CI is not strictly as in ICRU 62, since the

Fig. 1. Diagram of development of experimental treatment plans.

entire PTV is not always totally encompassed by the 95% isodose. Nevertheless, it remains a useful measure of the conformality of the proposed treatments¹⁷.

HI was calculated based on the formula: $((D_{2\%} - D_{98\%}) / D_{median})$ with zero indicating the ideal homogeneity since $D_{2\%}$ and $D_{98\%}$ are equal. D_{max} was reported for optic structures. $D_{40\%}$ for the left hippocampus, converted to biologically equivalent doses in 2-Gy fractions (EQD2) assuming an α/β ratio of 2 Gy, was recorded ($EQD_2^{40\%}$) (ref.¹²). All pertinent values were extracted from dose-volume histograms using an in house developed data mining software. Basic statistical methods including the Wilcoxon signed-rank test were used to obtain mean values and relative as well as absolute differences between HA-WBRT and experimental plans.

RESULTS

Hippocampus avoiding-WBRT ("baseline") treatment plans

HA-WBRT plans' characteristics are summarized in Table 1. All treatment plans met RTOG 0933 "per protocol criteria" for PTV coverage with mean CI 1.09 (range 1.08 - 1.1) and mean HI 0.21 (range 0.19 - 0.23). Mean value of near maximal dose in PTV was $D_{2\%} = 33$ Gy (RTOG 0933 limit is ≤ 37.5 Gy) with mean near minimal dose in PTV $D_{98\%} = 26.4$ Gy (RTOG 0933 limit is ≥ 25 Gy). All hippocampal dose-volume constraints were met ("per protocol criteria") with an exception in one patient where right as well as left hippocampal $D_{100\%}$ exceeded limit of 9 Gy (9.34 Gy and 10.07 Gy, respectively). The isodose treatment plan for one representative patient is presented in Fig. 2.

Left HA-WBRT ("BEST LH") treatment plans

For these experimental treatment plans, inverse planning was tailored to achieve the same PTV dosimetry as in "baseline" HA-WBRT. Resultant dosimetric characteristics are listed in table 2 along with absolute and relative differences between these data and mean parameters in "baseline" HA-WBRT. The right hippocampus is intentionally not spared leading to mean $D_{100\%} = 30.1$ Gy.

Table 1. Summary of treatment characteristics of HA-WBRT plans (effort to meet RTOG 0933 “per protocol” criteria).

Target / organ at risk	Mean (SD) “baseline”	RTOG 0933 criteria
PTV		
V _{100%}	90% (0)	90%
D _{2%}	33 Gy (0.08)	≤ 37.5 Gy
D _{98%}	26.4 Gy (0.29)	≥ 25 Gy
CI	1.09 (0.007)	
HI	0.21 (0.01)	
Optic nerves and chiasm		
D _{max}	33.7 Gy (0.48)	≤ 37.5 Gy
Hippocampus_right		
D _{100%}	7.8 Gy (0.56)	≤ 9 Gy
D _{max}	14 Gy (0.37)	≤ 16 Gy
Hippocampus_left		
D _{100%}	8.5 Gy (0.57)	≤ 9 Gy
D _{max}	13.8 Gy (0.21)	≤ 16 Gy
EQD ₂ ^{2Gy} 40%	8.24 Gy (0.4)

Fig. 2. Isodose treatment plan of representative HA-WBRT (A) and LHA WBRT (“BEST LH”) for the same patient (B). Dose is displayed in color wash with minimal dose of 80 % from prescribed dose.

Mean D_{100%} and D_{max} for the left hippocampus were significantly reduced by 11.2% ($P=0.005$) and 10.9 % ($P=0.005$) respectively. Moreover, left hippocampal EQD₂^{2Gy} 40% was significantly reduced from a mean value 8.24 Gy in “baseline” to the mean value of 6.82 Gy in “BEST LH” experimental plan ($P=0.005$). The isodose treatment plan for one representative patient is shown in Fig. 2.

Left HA-WBRT (“BEST PTV”) treatment plans

For these experimental treatment plans, inverse planning was tailored to achieve the same left hippocampus dosimetry as in “baseline” HA-WBRT. Resultant dosimetric characteristics are listed in table 3 along with absolute and relative differences between these results and mean parameters in “baseline” HA-WBRT. Homogeneity of PTV irradiation was significantly improved with the same

left hippocampal D_{100%} ($P=0.92$) and D_{max} ($P=0.39$) as in “baseline” plans. HI was reduced by 31.2% ($P=0.005$) mirrored by lower PTV_D_{2%} (-0.8 Gy, $P=0.005$) and higher PTV_D_{98%} (+1.3 Gy, $P=0.005$). No difference was observed in conformity index.

DISCUSSION

The potential of further decrease of hippocampal irradiation during unilateral hippocampal sparing WBRT is described in this planning study. This concept makes it possible to significantly reduce unilateral hippocampal D_{100%}, D_{max} and EQD₂^{2Gy} 40% with comparable target coverage as in “standard” HA-WBRT. Vice versa, it is possible to significantly improve target coverage with ac-

Table 2. Summary of treatment characteristics of Left HA-WBRT (“BEST LH”) treatment plans.

Target / organ at risk	Mean (SD) “BEST LH”	Absolute (relative) difference to “baseline” HA-WBRT
PTV		
V _{100%}	90% (0)	0 (0%)
D _{2%}	32.9 Gy (0.08)	-0.1 Gy (-0.2%)
D _{98%}	27.1 Gy (0.49)	+0.7 Gy (+2.7%)
CI	1.1 (0.004)	+0.01 (-0.7%)
HI	0.2 (0.02)	-0.03 (-12.0%)
Optic nerves and chiasm		
D _{max}	33.3 Gy (0.37)	-0.5 Gy (-1.4%)
Hippocampus_right		
D _{100%}	30.1 Gy (0.34)	+22.3 Gy (+286.8%)
D _{max}	32.9 Gy (0.39)	+19 Gy (+136%)
Hippocampus_left		
D _{100%}	7.6 Gy (0.68)	-0.9 Gy (-11.2%)
D _{max}	12.3 Gy (0.19)	-1.5 Gy (-10.9%)
EQD ₂ ^{2Gy} 40%	6.82 Gy (0.54)	-1.43 Gy (-17.4%)

Table 3. Summary of treatment characteristics of Left HA-WBRT (“BEST PTV”) treatment plans.

Target / organ at risk	Mean (SD) “BEST PTV”	Absolute (relative) difference to “baseline” HA-WBRT
PTV		
V _{100%}	90% (0)	0 (0%)
D _{2%}	32 Gy (0.07)	-0.8 Gy (-2.4%)
D _{98%}	27.8 Gy (0.42)	+1.3 Gy (+5%)
CI	1.09 (0.008)	+0.01 (+0.55%)
HI	0.15 (0.02)	-0.07 (-31.2%)
Optic nerves and chiasm		
D _{max}	32.7 Gy (0.39)	-1 Gy (-3%)
Hippocampus_right		
D _{100%}	29.6 Gy (0.29)	+21.8 Gy (+280.7%)
D _{max}	32.2 Gy (0.27)	+18.3 Gy (+131.1%)
Hippocampus_left		
D _{100%}	8.5 Gy (0.54)	+0.01 Gy (+0.2%)
D _{max}	13.7 Gy (0.33)	-0.1 Gy (-0.8%)
EQD ₂ ^{2Gy} 40%	8.22 Gy (0.53)	-0.02 Gy (-0.3%)

ceptance of the same unilateral hippocampal dosage as in “standard” HA-WBRT. Decreasing the hippocampal dose (D_{100%}) to as low as possible was shown to predict less decline in some memory tests over time in patients irradiated for brain metastases^{12,13}. More recently, white matter damage as well as thinning of the cerebral cortex after brain irradiation proved to be highly dose-dependent^{18,19}. Hippocampus itself demonstrates radiation dose-dependent atrophy after treatment for brain tumors^{20,21}. These dose-dependent brain changes are predicted to influence cognition and memory. Altogether, minimizing the dose within this critical part of the brain may be of high clinical relevance²². The risk of recurrence of brain metastases in undertreated regions is a reasonable trade-off especially in palliative irradiation.

Our previous study described significant decreases in hippocampal N-acetylaspartate concentration (marker of neuronal density and viability) following WBRT (ref.¹⁰).

However, only changes in the left hippocampus positively correlated with the decline in memory function¹¹. Another recent study of predictors for late neurocognitive dysfunction showed correlations of vascular dose-response in the left hippocampus in females with changes in memory function after radiotherapy⁹. Is it possible that only unilateral hippocampal radio-injury is responsible for subsequent neurocognitive decline? The functional anatomy of the cognitive domains suggests that verbal memory, the gold standard in evaluation of post radiotherapy cognitive impairment, often localize to the dominant hippocampus⁷. Nevertheless, it would be useful to at first know, whether and to what extent this radiotherapy approach translates into improvement in radiotherapy treatment plans.

In order to demonstrate the potential of LHA-WBRT, we created two types of experimental plans with different optimization intent. “BEST LH” treatment plans’

Fig. 3. Averaged dose-volume histogram from all patients presenting differences between “baseline” HA WBRT and “BEST LH” left hippocampus sparing WBRT treatment plans.

potential to further decrease left hippocampal dose with the same target coverage is showed in Fig. 3. The left hippocampal $\text{EQD}_2^{40\%}$ was significantly reduced from a mean value 8.24 Gy in “baseline” to mean 6.82 Gy in “BEST LH” experimental plan. This dosimetric parameter for both hippocampi was established by Gondi et al. with a threshold of 7.3 Gy; irradiation surpassing this value is associated with long-term impairment in list-learning delayed verbal recall in patients with benign or low-grade adult gliomas¹². “BEST LH” treatment optimization successfully undershot this threshold value. Although, we only assumed that the threshold value can be used for patients with brain metastases and for unilateral hippocampal sparing. Nevertheless, the slope of dose-response curve for $\text{EQD}_2^{40\%}$ suggests that doses of around 6 to 8 Gy are highly clinically important¹². For this reason, the decrease from 8.24 Gy to 6.82 Gy as observed in our planning study may be clinically relevant. Altogether, even if this reduction would not further decrease cognitive impairment (suggesting the dominant role of left hippocampus), with full irradiation of right hippocampus, the risk of subsequent development of hippocampal or perihippocampal metastases is reduced by one half. This risk is generally considered low because only 1.6% of brain metastasis extend to the hippocampus itself²³.

There are several limitations in our study, which are mainly related to the nature of planning studies in general. Among others, comparison of PTV dosimetry between “baseline” HA-WBRT plan and two experimental LHA-WBRT plans is biased due to different definition of PTV. This is because in LHA-WBRT plans, the right hippocampus was integrated to PTV. Another already mentioned limitation is in adaptation of hippocampal dose-volume constraints from studies of primary gliomas ($\text{EQD}_2^{40\%}$).

The inherent limitation may be the fundamental question whether there is a role for WBRT in up-to-date treatment of brain metastases and with higher availability of systems for stereotactic radiosurgery²⁴⁻²⁶. From one perspective, the best technique for sparing the hippocampus is avoidance of WBRT itself and proceeding with stereo-

tactic radiotherapy. Clearly, the role of WBRT is changing and more data from ongoing clinical trials are needed to establish the best treatment recommendations for defined subsets of patients²⁷.

CONCLUSION

Unilateral hippocampal sparing during WBRT could improve target coverage and/or further reduce the dose to the spared hippocampus. Whether reduction in left hippocampus dosage as described in our planning study would further reduce post radiotherapy side effects warrants further research. Only future clinical trials can confirm whether statistically significant reduction in left hippocampal dose is also clinically significant.

ABBREVIATIONS

WBRT: whole brain radiotherapy; HA-WBRT: hippocampus avoiding whole brain radiotherapy; LHA-WBRT: left hippocampus avoiding whole brain radiotherapy; PTV: planning target volume; MRI magnetic resonance imaging; PRV planning organ at risk volume; VMAT: volumetric arc therapy.

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REFERENCES

- Gondi V, Tomé WA, Mehta MP. Why avoid the hippocampus? A comprehensive review. *Radiother Oncol* 2010;97(3):370-6.
- Kazda T, Jancalek R, Pospisil P, Sevela O, Prochazka T, Vrzal M, Burkon P, Slavik M, Hynkova L, Slampa P, Laack NN. Why and how to spare the hippocampus during brain radiotherapy: the developing role of hippocampal avoidance in cranial radiotherapy. *Radiat Oncol* 2014;9:139.
- Awad R, Fogarty G, Hong A, Kelly P, Ng D, Santos D, Haydu L. Hippocampal avoidance with volumetric modulated arc therapy in melanoma brain metastases - the first Australian experience. *Radiat Oncol* 2013;8:62.
- Marsh JC, Godbole R, Diaz AZ, Gielda BT, Turian JV. Sparing of the hippocampus, limbic circuit and neural stem cell compartment during partial brain radiotherapy for glioma: a dosimetric feasibility study. *J Med Imaging Radiat Oncol* 2011;55(4):442-9.

5. Marsh JC, Ziel GE, Diaz AZ, Wendt JA, Gobole R, Turian JV. Integral dose delivered to normal brain with conventional intensity-modulated radiotherapy (IMRT) and helical tomotherapy IMRT during partial brain radiotherapy for high-grade gliomas with and without selective sparing of the hippocampus, limbic circuit and neural stem cell compartment. *J Med Imaging Radiat Oncol* 2013;57(3):378-83.
6. Kazda T, Pospíšil P, Doleželová H, Jančálek R, Slampa P. Whole brain radiotherapy: Consequences for personalized medicine. *Rep Pract Oncol Radiother* 2013;18(3):133-8.
7. Lee TM, Yip JT, Jones-Gotman M. Memory deficits after resection from left or right anterior temporal lobe in humans: A meta-analytic review. *Epilepsia* 2002;43(3):283-91.
8. Jalali R, Mallick I, Dutta D, Goswami S, Gupta T, Munshi A, Deshpande D, Sarin R. 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(4):974-9.
9. Farjam R, Pramanik P, Aryal MP, Srinivasan A, Chapman CH, Tsien CI, Lawrence TS, Cao Y. A Radiation-Induced Hippocampal Vascular Injury Surrogate Marker Predicts Late Neurocognitive Dysfunction. *Int J Radiat Oncol* 2015;93(4):908-15.
10. Pospíšil P, Kazda T, Bulik M, Dobiaskova M, Burkon P, Hynkova L, Slampa P, Jancalek R. Hippocampal proton MR spectroscopy as a novel approach in the assessment of radiation injury and the correlation to neurocognitive function impairment: initial experiences. *Radiat Oncol* 2015;10:211.
11. Pospíšil P, Kazda T, Hynkova L, Bulik M, Dobiaskova M, Burkon P, Laack NN, Slampa P, Jancalek R. Post-WBRT cognitive impairment and hippocampal neuronal depletion measured by in vivo metabolic MR spectroscopy: Results of prospective investigational study. *Radiother Oncol* 2017;122(3):373-9.
12. Gondi V, Hermann BP, Mehta MP, Tomé WA. Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. *Int J Radiat Oncol Biol Phys* 2013;85(2):348-54.
13. Gondi V, Pugh SL, Tomé WA, Caine C, Corn B, Kanner A, Rowley H, Kundapur V, DeNittis A, Greenspoon JN, Konski AA, Bauman GS, Shah S, Shi W, Wendland M, Kachnic L, Mehta MP. Preservation of Memory With Conformal Avoidance of the Hippocampal Neural Stem-Cell Compartment During Whole-Brain Radiotherapy for Brain Metastases (RTOG 0933): A Phase II Multi-Institutional Trial. *J Clin Oncol* 2014;32(34):3810-6.
14. Hippocampal contouring: a contouring Atlas for RTOG 0933. Available from: [http://www.rtog.org/LinkClick.aspx?fileticket=59vaU8vfgQc%3d&tabid=338]
15. Gondi V, Tolakanahalli R, Mehta MP, Tewatia D, Rowley H, Kuo JS, Khuntia D, Tomé WA. 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(4):1244-52.
16. Scoccianti S, Detti B, Gadda D, Greto D, Furfaro I, Meacci F, Simontacchi G, Di Brina L, Bonomo P, Giacomelli I, Meattini I, Mangoni M, Cappelli S, Cassani S, Talamonti C, Bordi L, Livi L. Organs at risk in the brain and their dose-constraints in adults and in children: A radiation oncologist's guide for delineation in everyday practice. *Radiother Oncol* 2015;114(2):230-8.
17. Bolsi A, Fogliata A, Cozzi L. Radiotherapy of small intracranial tumours with different advanced techniques using photon and proton beams: a treatment planning study. *Radiother Oncol* 2003;68(1):1-14.
18. Connor M, Karunamuni R, McDonald C, White N, Pettersson N, Moiseenko V, Seibert T, Marshall D, Cervino L, Bartsch H, Kuperman J, Murzin V, Krishnan A, Farid N, Dale A, Hattangadi-Gluth J. Dose-dependent white matter damage after brain radiotherapy. *Radiother Oncol* 2016;121(2):209-16.
19. Karunamuni R, Bartsch H, White NS, Moiseenko V, Carmona R, Marshall DC, Seibert TM, McDonald CR, Farid N, Krishnan A, Kuperman J, Mell L, Brewer JB, Dale AM, Hattangadi-Gluth JA. Dose-Dependent Cortical Thinning After Partial Brain Irradiation in High-Grade Glioma. *Int J Radiat Oncol Biol Phys* 2016;94(2):297-304.
20. Seibert TM, Karunamuni R, Bartsch H, Kaifi S, Krishnan AP, Dalia Y, Burken J, Murzin V, Moiseenko V, Kuperman J, White NS, Brewer JB, Farid N, McDonald CR, Hattangadi-Gluth JA. Radiation Dose – Dependent Hippocampal Atrophy Detected With Longitudinal Volumetric Magnetic Resonance Imaging. *Int J Radiat Oncol* 2017;97(2):263-9.
21. Balentova S, Hajtmanova E, Filova B, Borbelyova V, Lehotsky J. Effect of Fractionated Irradiation on the Hippocampus in an Experimental Model. *Klin Onkol* 2015;28(3):191-9.
22. Tomé WA, Gökhan Ş, Gulinello ME, Brodin NP, Heard J, Mehler MF, Guha C. Hippocampal-dependent neurocognitive impairment following cranial irradiation observed in pre-clinical models: current knowledge and possible future directions. *Br J Radiol* 2016;89(1057):20150762.
23. Lakomy R, Hynkova L, Pospíšil P, Burkon P, Slavik M, Slampa P, Jancalek R, Kazda T. Patterns of failure after brain metastases radiotherapy: reflections on the importance for treatment and clinical trials reporting. *Neoplasma* 2017 Mar 3. [Epub ahead of print] doi: 10.4149/neo_2017_302
24. Fogarty GB, Hong A, Gondi V, Burmeister B, Jacobsen K, Lo S, Paton E, Shivalingam B, Thompson JF. Debate: adjuvant whole brain radiotherapy or not? More data is the wiser choice. *BMC Cancer* 2016; 16:372.
25. Mehta MP, Aoyama H, Gondi V. The Changing Role of Whole-Brain Radiotherapy: Demise or Time for Selective Usage? *JAMA Oncol* 2017 Jan 5 [Epub ahead of print] doi: 10.1001/jamaoncol.2016.5414
26. Matzenauer M, Vrana D, Vlachova Z, Cwiertka K, Kalita O, Melichar B. Radiotherapy management of brain metastases using conventional linear accelerator. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2016;160(3):412-6.
27. Soltys SG, Kirkpatrick JP, Laack NN, Kavanagh BD, Breneman JC, Shih HA. Is Less, More? The Evolving Role of Radiation Therapy for Brain Metastases. *Int J Radiat Oncol* 2015;92(5):963-6.