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REVIEW ARTICLE

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Benefits and difficulties during brain radiotherapy planning with hippocampus sparing

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ABSTRACT

Radiotherapy (RT) is frequently used in the treatment of primary and secondary brain tumours, as well as in prophylactic cranial irradiation (PCI). The hippocampus plays a key function in the process of remembering, relaying information from short-term to long-term memory as consolidation, and spatial orientation. Sparing the hippocampus during brain radiotherapy aims to prevent hippocampal-dependent cognitive function deterioration. This procedure requires a good knowledge of the brain's radiological anatomy and use of modern radiotherapy techniques.

This article presents the validity of hippocampus sparing during brain radiotherapy, the potential benefits of using this procedure, available clinical premises regarding patient qualification, and technical difficulties in the brain's RT planning with hippocampus avoidance.

Key words: hippocampus sparing, brain radiotherapy, cognitive function

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Hippocampus

The hippocampus was first described by Arantius in 1587 as a grey matter brain zone resembling a creature from Greek mythology drawing the chariot of the god of the sea, Poseidon. It consists of the head with the appearance of a horse's head and a curved body like a sea wave. Hence the name of this organ is derived from *hippo* (horse) and *campi* (turn) [1]. It is difficult to depict the shape of the hippocampus in a two-dimensional plane due to its long, curved body (Fig. 1A, 1B).

Anatomically, the hippocampus is an even organ located in telencephalon region, in the temporal lobes of the cerebral cortex of the right and left hemispheres of the brain. Within the hippocampus, in the vicinity of the dentate gyrus, there is a cluster of neural stem cells (NSCs) grouped in two niches: the subventricular zone (SVZ) and the subgranular zone (SGZ) [2, 3] (Fig. 2). These NSCs are responsible for the key functions of this structure. It is worth noting that they are very sensitive to damaging factors such as ischaemia, stress, and ionising radiation [4]. An analysis of brain magnetic resonance imaging (MRI) of 58 patients with nasopharyngeal carcinoma performed three and six months after completed brain RT revealed atrophy of the hippocampal area [5]. Depopulation of NSCs by apoptosis, which occurs after the activation of the damaging factor, appears already after 12 hours and leads to the manifestation of deficits in cognitive functions for which the hippocampus corresponds, and in particular to disorders in memorising and reproduction of information from working memory [6–8]. It was shown that irradiation of the hippocampus area with doses close to 30 Gy and higher, given in conventional fractionation, causes a decrease in NSCs proliferation by 93–96% after 48 hours [7]. Deficits in cognitive functions appear about two months after the activation of the damaging factor, and the peak of intensity falls around the fourth month [9–12]. Importantly, the consequences of NSC apoptosis are irreversible and usually progressive over time.

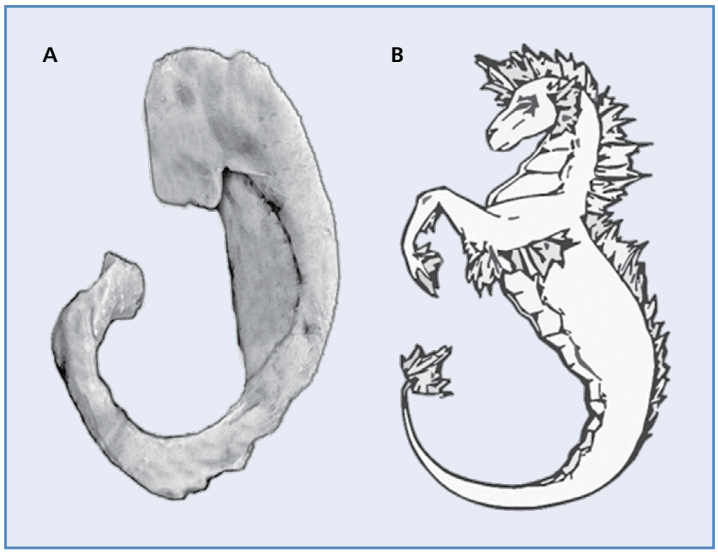

Figure 1. The anatomical shape of the hippocampi (A) and a sketch of the creation from Greek mythology (B) (author: M. Filippow)

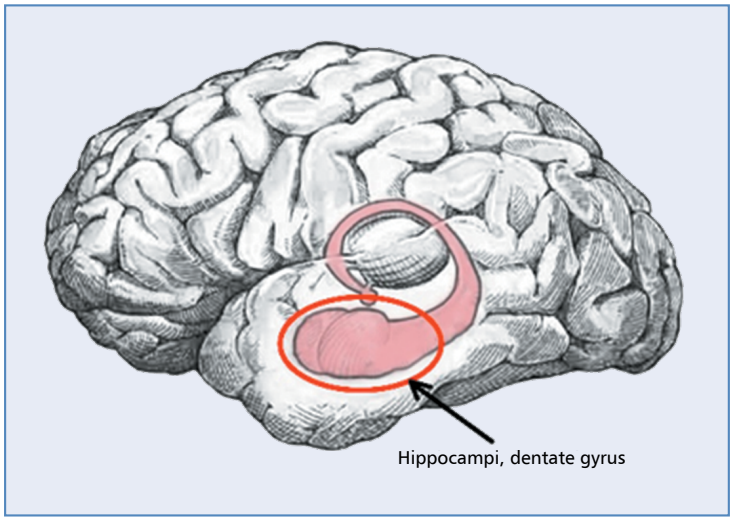

Figure 2. Localisation of neural stem cell (NSC) compartment in the region of dentate gyrus of hippocampi (author: M. Filippow)

The rationale of hippocampus contouring during brain CT planning

The majority of patients with malignant neoplasms within the brain manifest cognitive dysfunction even before the implementation of any causative treatment. They may result from the presence of malignant disease within the brain, its progression, the use of supportive treatment (e.g. opioids, steroids), comorbidities, or advanced age [13, 14]. Sudden/acute deterioration of cognitive functions may appear just after the brain's RT due to the presence of brain metastases accompanied by extensive oedema zones around changes [15]. In turn, it was demonstrated that patients with small-cell lung cancer (SCLC) without metastases in the brain may show deterioration of cognitive functions based on a previously unknown mechanism, presumably as a paraneoplastic effect [16]. The progress in oncological treatment is reflected both in the quality of therapy and in its effectiveness, which translates into longer survival time. Recently, attention has been paid to the patient's quality of life after the use of anti-cancer treatment, and attempts are being made to reduce the negative effects of the therapy. Irradiation of the brain, particularly the area of the hippocampus, may lead to further cognitive deficits, which as a result significantly affects patients' quality of life. Described cognitive functions relate to the thought processes used to process information coming from the outside world into the mind and contain basic aspects such as memory, attention, and association and complex ones, which include thinking and imagination [17].

The most frequently described deficits of cognitive functions after brain CT are losses in short-term memory and less frequently in delayed memory, and problems with information recall and learning [18, 19]. There are also described verbal memory disorders, necessary to understand reading text, as well as inhibition of the higher cognitive processes necessary to behave in new and difficult situations [20, 21]. It is worth noting that any deterioration of cognitive functions in oncological patients significantly affects the quality of life after the completion of anticancer treatment and can contribute to the deepening of lowered mood, and even the occurrence of depressive episodes [22, 23].

It should be noted that the hippocampus is a very rare location of cancer metastases [24, 25]. Researchers from the University of Wisconsin documented that only 3.3% of intracranial metastatic lesions were located up to 5 mm from the hippocampus, and over 86% were located at least 15 mm from this structure [26]. In another retrospective study analysing the location of 697 intracranial metastases, only 2.2% of lesions were found in the direct location of the hippocampus, and in patients with oligometastatic disease (one to three brain metastases) the rate of hippocampal metastases was below 1% [25].

Clinical assessment of impaired cognitive functions

Evaluation of the cognitive deficit after brain CT is methodically difficult and ambiguous. Until now, researchers have used subjective methods in the form of psychological tests, e.g. MMSE (mini-mental stage examination), HVLT (Hopkins verbal learning test), and AVLT (auditory verbal learning test) [10, 12, 27]. An example is the RTOG 0914 study conducted in a group of 445 patients with brain metastases (BM), who underwent whole brain radiotherapy (WBRT), which proved that both hypofractionated (30 Gy/10 fractions) and conventional (40 Gy/20 fractions) RT lead to a significant reduction in cognitive function, and the results of the MMSE test revealed a marked deterioration in cognitive functions in both groups two and three months after completion of RT [9]. Another multicentre phase III trial based on 401 patients with BM treated with WBRT (30 Gy/10 fractions) revealed a significant decrease in cognitive functions assessed on the basis of the verbal fluency test (COWA, controlled oral word association) four months after RT, and then their improvement 15 months after completion of RT [28]. Preliminary results of the phase II RTOG 0933 study, using Hopkins' verbal learning test (HVLT) showed that the use of hippocampal sparing in patients with BM during WBRT resulted in lower intensity of early cognitive deficits within the first four months of treatment versus the state before treatment, as compared to RT without the cover of this structure [10, 12]. Another study, using the HVLT test, showed a smaller loss of cognitive functions in the field of learning and short-term memory in patients with 1–3 BM, who underwent only stereotactic brain radiotherapy (SRT), in comparison to patients with WBRT [12]. In turn, the AVLT auditory test revealed a decrease in verbal memory 6–8 weeks after completion of WBRT in patients with BM, in comparison to baseline status [12]. In the phase III RTOG 0214 study conducted in a group of patients with stage III non-small cell lung cancer (NSCLC) subject to PCI, a marked decrease in cognitive function was seen after three months of brain RT evaluated with the MMSE test [27]. Research is ongoing to find an objective biomarker used alone or in fusion with MRI to detect early damage in the hippocampal region [5].

Hippocampus contouring techniques

Manual contouring of the hippocampus

This is the most popular technique in the daily practice of a radiotherapist; however, it requires a good knowledge of anatomy in the planned area. Correct contouring of the hippocampus is the most important process during the preparation of an irradiation plan with a procedure for the protection of this structure. In any case of contouring of the hippocampus, it is necessary to fuse locational computed tomography images with a current T2-weighted MRI brain examination at a scan density of min. every 1.5 mm [1]. The atlas created by the RTOG group is an assistance in the process of contouring the hippocampus during brain RT planning [29]. The necessity of training in contouring is emphasised, which allows practice of the technique of contouring of the most important area within the hippocampus: the dentate gyrus [30]. It was shown that without "contouring learning" of this structure there are large discrepancies in the exact location of this region between radiotherapists, and hence inconsequence in planning the brain RT and suboptimal results of treatment. The biggest discrepancies during manual contouring of the hippocampus occur in the area of the horn of the anterior lateral ventricle, while the smallest are in the area of the brain stem [31].

Automatic contouring of the hippocampus

Automatic methods of brain segmentation are usually based on MRI images obtained on 1.5 T, 3 T, and even 7 T cameras, for better imaging and contrast of individual structures [32]. The first group includes pro-

grams based on atlases, i.e. Atlas-Based Segmentation, Multi-Atlas-Based Methods [33, 34]. The second group of methods are modern computer programs analysing voxels, such as the Auto-Context Model (ACM) [35]. The automatic program for contouring the hippocampus during RT planning has advantages and disadvantages. The advantages undoubtedly include the minimum contribution of the "radiotherapist's hand" and the accuracy of contouring on MRI images. However, it should be remembered that such contouring should always be verified and approved by a radiotherapist, which is connected with the requirement of his/her knowledge not only of the radiological anatomy of the brain, but also of the influence of various pathologies on its morphology [36, 37]. Automatic atlases for contouring of structures are becoming more common; however, most radiotherapy departments still do not have such software that is optimally integrated with the RT planning system. Importantly, this is also associated with the additional costs of purchasing such software.

It is worth noting that the brain often has various pathologies that disturb the anatomy of its structures, such as microcalcifications, the number of which increases with age, states after strokes, seizures, after brain infections or Alzheimer's disease [38–40]. In such cases, the automatically contoured structures of the hippocampus may turn out to be incorrect.

Clinical situations in which hippocampal protection should be considered during RT planning

In clinical practice, an appropriate group of patients should be selected in which there is a need for avoiding of the hippocampus during brain RT planning. The above procedure is a technical challenge regarding application of highly specialised RT techniques. It can be considered for patients with primary cerebral tumours, where the use of intensity-modulated radiation therapy (IMRT) allows us to reduce the dose within the hippocampus by 56.8% in relation to the classical 3D technique, i.e. from 36.6 Gy to approx. 15 Gy in the case of irradiation of part of the brain in the aforementioned group of patients [41]. In certain clinical situations, i.e. in the presence of an extensive oedema or central tumour location, especially around the brain stem, many authors suggest shielding only one hippocampus — on the opposite side of the tumour site [20, 42, 43]. It is worth adding that in children primary brain tumours are diagnosed much more frequently than in adults, and the procedure of hippocampal protection in these cases has a special clinical value during RT planning [44, 45].

Patients with SCLC represent another population. Elective brain radiotherapy — PCI with hippocampal sparing may be considered in patients with radical radio-chemotherapy or in patients undergoing palliative chemotherapy, who have achieved a clinical response within the chest after this treatment with no disease progression [46, 47]. The most frequently recommended PCI regimen is whole brain irradiation to a total dose of 25 Gy in 10 fractions of 2.5 Gy [48]. It has also been demonstrated that PCI may contribute to the impairment of cognitive functions as a result of post-radiation depopulation of NSCs within the hippocampus [49, 50]. Research results indicate that the use of a cover of both hippocampi could reduce or even prevent cognitive complications after PCI [49, 51].

Patients with secondary brain tumours (BM) constitute the most controversial group in terms of application of hippocampal protection procedure, due to the shortest expected overall survival, and therefore a relatively short time of expected potential benefit. On the other hand, the majority of research on the hippocampus protection procedure during cerebral irradiation concerns patients with BM. Unfortunately, the current results of the study do not allow us to clearly define the eligibility criteria for the hippocampus protection procedure during brain RT in the above group of patients [52–54].

There is a need to select specific criteria for the qualification of patients for hippocampus protection procedure during brain RT and to develop practical recommendations during this procedure within brain RT.

"Protective" doses of ionising radiation in the area of the hippocampus

In current research it has been shown that even small doses of ionising radiation cause radiation-induced inflammation of the areas of neurogenesis within the hippocampus [6, 7]. In the phase II RTOG 0933 study a dose of ionising radiation was initially proposed that should not be exceeded in the hippocampal area during PCI and WBRT planning (Table 1) [54]. The above recommendations may prevent deterioration in terms of memory, especially short-term memory and verbal memory, or the reproduction of freshly-stored information after application of RT to the cerebral region [58]. The proposed doses refer to conventional radiotherapy in which the fractional dose oscillates between 2 and 3 Gy. The problem arises in the case of hypofractionated RT and in particular stereotactic RT, although there are newer reports of "protective" doses in the hippocampus region in such cases [59, 60].

Summary

Brain radiotherapy is a recognised method of oncological treatment in patients with primary and meta-

Table 1. Ionising radiation doses (Gray — Gy) recommended for hippocampal sparing brain irradiation (WBRT, PCI) procedure, according to the RTOG 0933 study compared to other authors. The ranges of standards are given in brackets

	RTOG 0933 [54, 58]	Gondi et al. [55]	Nevelsky et al. [53]	Wang et al. [37]	Krayenbuehl et al. [56]	Zhao et al. [57]
PTV D98% (Gy)	≥ 25		25.7 (25.4–25.9)		25.8 (25.0–27.1)	≥ 25*
PTV V95% (%)		96.9 (96.1–97.5)		96.9 (96.0–97.5)	96.4 (95.2–97.8)	
PTV D2 (Gy)	≤ 37.5		37.2 (36.9–37.6)	35.1 (34.8–35.6)	33.5 (32.8–34.6)	
PTV V30Gy (%)	= 90		92.1 (90.5–93.2)		92 (92.0–92.0)	< 23.75
Hippocampus D100% (Gy)	≤ 9		8.4 (7.7–8.9)	9.3 (8.3–10.0)	8.1 (7.8–8.5)	≤ 9
Hippocampus D_{mean} (Gy)		7.3 (7.2–7.6)			7.3 (6.0–7.9)	
Hippocampus D_{max} (Gy)	≤ 16	15.3 (14.3–15.9)	14.3 (13.5–15.4)	16 (14.6–16.9)	14.1 (12.0–15.3)	≤ 16
Lens D_{max} (Gy)		3.8 (3.1–4.3)		5.8 (4.5–6.5)	4.6 (3.7–5.6)	
Crossing of the optic nerves (optic chiasm) D_{max} (Gy)	≤ 37.5		36.2 (33.9–37.2)	34.7 (33.1–36.8)	32.9 (31.7–35.1)	
Optic nerve D_{max} (Gy)	≤ 37.5		32.5 (28.3–35.7)	32.0 (23.7–36.1)	33.1 (32.5–33.8)	

*PCI-PTV — planning target volume with 3 mm margin excluding the hippocampal region (hippocampus expanded by 5 mm); PCI — prophylactic cranial irradiation; WBRT — whole brain radiation therapy; PTV — planning target volume; D_{max} — maximal point dose; D_{min} — minimal point dose; D_{mean} — mean point dose; D100% — dose to 100% of the volume; D98% — dose to 98% of the volume; V95% — volume covered by 95% of the prescribed dose; D2% — dose to 2% of the volume; V30Gy — volume covered by 30% of the prescribed dose

static cerebral lesions, although cognitive impairment appearing after this treatment may contribute to the deterioration of patients' quality of life. Occurrence of these complications is associated with post-radiation damage to the hippocampus, a structure particularly sensitive to ionising radiation, and especially the NSCs within it. Cognitive deficits mainly concern problems with memorising and reproducing information, and problems with short-term, delayed, and verbal memory. Application of the hippocampus protection procedure during brain RT may significantly reduce or even prevent the above complications.

Modern RT techniques provide the ability to protect the hippocampus during brain RT, although there is a need for further research to establish clinical indications, qualify the appropriate group of patients, and develop technical recommendations for the implementation of this procedure, which could translate into clinical benefits and improve the quality of radiotherapy (quality assurance).

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