

Hippocampal sparing in brain radiotherapy

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Radiotherapy is one of the principal methods for treating brain cancer. Over recent years, a decline in patient quality of life has increasingly been observed in those undergoing brain irradiation, where hippocampal-dependent cognitive function has become impaired.

The hippocampus is a paired structure of the limbic system situated in the medial temporal lobes of the telencephalon. Preliminary findings suggest that irradiation damaged neural stem cells in the hippocampus undergo apoptosis, resulting in deteriorating cognitive function.

Despite the technical aspects for affording hippocampal avoidance during irradiation, much controversy still surrounds the techniques that shield the hippocampus without reducing the benefits of the intended radiotherapy for a given clinical condition. Furthermore, a tolerated radiation dose sufficient for preserving neural stem cell function has not been yet established.

Delivering a method for an unequivocal assessment of cognitive function, post-irradiation, is also fraught with difficulty. Hitherto, only subjective psychological testing have been applied such as MMSE, HVLT or AVLT methods. Objective methods for optimally determining radiation-induced injury to the hippocampal region are still being investigated.

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Introduction

Brain tumours constitute a considerable clinical problem because they affect this vital organ of the human body and where choosing an effective and safe treatment poses many challenges. During recent decades, morbidity rates for primary brain tumours in Poland have increased with around 3000 cases now reported annually. This represents 2% of all cancers for both genders and the average age at diagnosis is between 50 and 60 years. Brain metastases (BMs) are twice more likely to occur than primary brain tumours, at rates of around 15%–20% in all those adult patients with cancers of varying origin. In children however, cases of BM account for only 0.5% of all brain cancer [1].

One of the basic methods for treating patients suffering brain cancer, both primary and secondary, is by radiotherapy (RT). The advantages of using RT over other therapeutic methods are, amongst others, the possibility of eliminating

not only the macroscopically visible tumour, but also the micro-foci (eg. in cases of prophylactic cranial irradiation in patients with small cell lung cancer), treating patients with multiple BMs or anticancer treatment of patients diagnosed with inoperable brain tumours. Furthermore, the presence of the blood-brain barrier does not compromise the effectiveness of RT, in contrast to those chemotherapeutic agents which are insufficiently capable of crossing this barrier. In planning brain RT, due consideration must be taken of many critical structures, termed 'Organs at Risk' (OAR) which are especially sensitive/susceptible to ionizing radiation. These include, amongst others, lenses, optic nerves and cross-over junction between the optic nerves and brain stem. Advanced RT techniques enable a more improved confocal beam radiotherapy directed towards the RT target area, whilst sparing critical structures which play special roles whenever tumours are located within the brain.

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In patients with primary brain tumours, RT is applied to a precisely delineated area restricted to the tumour or the tumour bed (+/- swelling of the tissues around the tumour, +/- margin of tissue surrounding the tumour). Quite often clinical circumstances dictate irradiating an extensive area of the brain (eg. in cases of infiltrating high malignant grade gliomas) which may lead a deteriorating quality of life for patients after treatment. It should however be stressed that using combination therapy in patients with brain tumours increases the chances of an ever longer survival. An example is afforded by patients suffering from *glioblastoma multiforme* (*glioblastoma*), where the combination of surgical treatment with adjuvant chemoradiotherapy improves local control (LC) and extends overall survival (OS) [2]. At the same time, patients undergoing antineoplastic therapy are more likely to suffer from worsening psychomotor dysfunction.

A slightly different situation exists for patients with metastases diagnosed as having just single BMs, in the absence of extracranial metastatic disease. In such cases, the risk of the brain treatment failing is relatively small which for most clinical situations, with suitably small volume metastases, makes possible the irradiation of the tumour metastasis by using stereotactic techniques of radiotherapy/radiosurgery (SRT/SRS) instead of undergoing whole brain RT (i.e. WBRT). By such means, the adverse effects of RT are lessened [3]. In cancer patients with current BM and extracranial metastases, the potential benefits from adding WBRT to SRT nevertheless outweigh their adverse effects [4].

Through using WBRT on BM patients the risk of disease progression in the brain becomes reduced, thereby improving patient Quality of Life (QoL) and in some cases extending their OS [5–8]. Despite this, there is a loss of neurocognitive function post-WBRT that is manifest and intensified, the longer the survival time of patients becomes [9, 10]. A number of prospective randomised clinical trials have demonstrated that WBRT improves LC patients with BM [5–7] but that its adoption is associated with declining QoL in terms of cognitive function when compared to the pre-treatment status [11].

The term 'cognitive function' refers to those mental processes responsible for information processing which inputs from the external environment and is internalised in the mind, that enables knowledge acquisition through interpreting reality and is essential for normal mental function. The basic cognitive functions are perception, attention and memory, whilst complex ones include thinking and imagination [12].

Deficits in cognitive function post-RT of the brain are apparent primarily as a short-term memory loss manifested as verbal memory dysfunction, problems with learning and being able to utilise newly acquired information [13, 14]. The process of memorising is closely linked to the functioning of granule cells from the hippocampal dentate gyrus [15].

The hippocampus as an organ at risk

The hippocampus is a twinned component of the limbic system located in the telencephalon within the temporal lobes of the cerebral cortex neighbouring the lateral ventricles (Fig.1). It plays a key role, inter alia, in learning, remembering, creating memories and relaying information from short-term to long-term memory together with the ability of remembering information [16]. The so-called neural stem cells (NSCs) are responsible for such functions and are located in the granular zone of the dentate gyrus within the hippocampus, which are the only brain cells possessing mitotic potential [17]. These cells in adult mammal brains are concentrated around only two niches: the subventricular zone (SVZ) of the anterolateral recess and the subgranular zone (SGZ) of the dentate gyrus within the hippocampus (Fig.1).

Maintaining cellular homeostasis in the hippocampus enables NSCs to undergo: proliferation, differentiation, normal cell function and apoptosis [18]. A year after birth, the numbers of NSCs in the human brain rapidly fall, after which, in subsequent years of childhood and adulthood they decrease at a more measured pace [19–21]. These cells proliferate in the subgranular zone, and then migrate circumferentially, becoming integrated with mature granular cells of the dentate gyrus within the hippocampus, and then mature into fully functional nerve cells [22]. In the human adult, NSC proliferation assures the formation of around 700 new nerve cells daily and that 1.75% of all neurones are replaced by new ones [23]. There are reports of NSCs migrating from the hippocampus to more remote area of the brain to replace damaged astrocytes or oligodendrocytes by transforming themselves into the given cell type [24, 25] (Fig.2).

NSCs are sensitive to various injuring factors, such as ischemia, stress or ionizing radiation [26]. Indeed, studies performed on mice have shown that ionizing radiation induces breakage of double-stranded DNA in NSC precursor cells leading to apoptosis [26]. This RT-dependent loss of NSCs leads to a deficient cognitive function, especially disorders of learning and memory [27–29]. In studies on young rats and mice subjected to brain RT, most of the enhanced NSC apoptosis in the hippocampus occurred after 12 hours post-RT [28, 30], thus indicating radiation-dependent suppression of neurogenesis in precursor NSCs [27, 31, 32].

It is therefore considered that in patients having undergone WBRT, then the observed impairments to learning, memory or spatial processing are the result of damage to the NSCs from the hippocampal dentate gyrus [33]. Interestingly, Mahajan et al. [34] found that damage to the left hippocampus during RT for brain cancer results in impaired learning and delayed recall, however there was no such correlation when tumours from the right side were subjected to RT [35]. The IQ (Intelligent Quotient) was found to decline in patients two years after undergoing conformal SRT (54

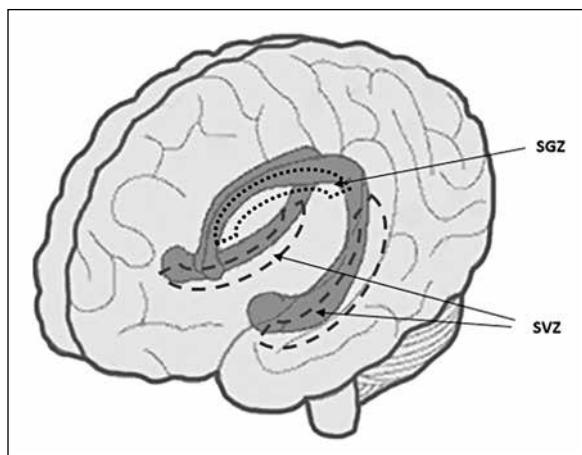


Figure 1. Lower Neural Stem Cells (NSCs) within the hippocampus

Gy in 30 fractions), whenever a radiation dose exceeded 42.5 Gy and was given to more than 13% by volume of the left temporal lobe, when compared to the pre-treatment status [35].

A study by Monje et al. [36] demonstrated that NSCs neurogenesis becomes inhibited by inflammation in the hippocampus through damage to the actinic granular zone of the dentate gyrus. Subsequent studies by this group conducted on rats revealed that the levels of dose fractionation and neurogenesis were correlated; i.e. a single fractional dose of 10 Gy induced a 62% decrease in the NSC proliferation rate whilst reducing the severity of neurogenesis by 97% within the hippocampal area when compared to the effects achieved by a single dose of 5 Gy which, according to this study, was found to be the damage limiting dose for NSCs [36, 37].

From the radiobiological viewpoint, the effect of ionizing radiation on the hippocampus is not completely understood and remains still debateable. According to the QUANTEC study (Quantitative Analysis of Normal Tissue Effects in the Clinic), the brain α / β ratio/index is 2.9 [39] but this is not explicitly specified for the hippocampus. Some investigators take an α / β ratio of between 2 and 3 for the hippocampus [40], whilst others use a value of 10 for hippocampal NSCs; the same as for stem cells [41, 42]. It is worth emphasising that preclinical experiments have demonstrated that doses of even 2 Gy cause apoptosis in NSCs [27, 43], thereby reducing the survival of these cells by even 50% [44].

Because of the key role that NSCs play (from the hippocampal dentate gyrus) in neurogenesis [45–48], any brain irradiation caused losses result in impaired cognitive function, especially that of memory [27, 49– 53]. In a 18-month follow-up study on patients with benign or low-grade glioma subjected to SRT, Gondi et al. [44] showed that the higher dose of 7.3 Gy (normalised to an equivalent dose of 2

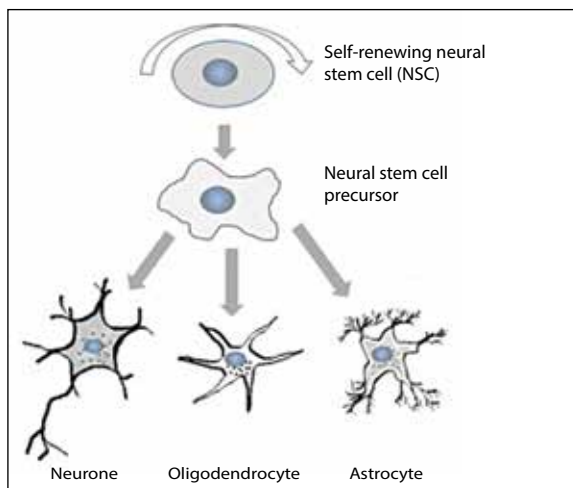


Figure 2. Neurogenesis of Neural Stem Cells

Gy) applied to at least 40%, by volume, of the hippocampus causes damage to the NSCs — resulting in problems with memory and learning.

Onset time of cognitive dysfunction, after brain RT

Those patients fortunate to experience long-term survival (i.e. over 12 months) were found to suffer from late side effects after brain RT, especially from the hypofractionated type, which were manifested mainly by dementia and psychomotor slowing [54]. Only after 2000, did cognitive function begin to be carefully evaluated following brain RT through using specialized psychological testing.

A RTOG 0914 study on 445 BM patients undergoing WBRT demonstrated that both RT hypofractionation (30Gy/10fr) as well as conventional RT (40Gy/20fr) lead to a significant reduction in cognitive function. Using the 'Mini Mental Stage Examination' (MMSE) a clear decline in cognitive function was observed in both groups after the 2nd and 3rd month post-RT [55].

In a multicenter phase III study on 401 BM patients undergoing WBRT (30Gy/10fr), a significant decline in cognitive function was demonstrated based on a test of verbal fluency 'Controlled Oral Word Association' (COWA) in the 4th month after RT, which then improved after 15 months post-RT [56]. In the Phase II RTOG 0933 study, a verbal learning material test was used, i.e. the 'Hopkins Verbal Learning Test' (HVLT), which showed that when the hippocampus is spared in BM patients during WBRT, then there is a less severe early loss of cognitive function already within the first 4 months after the RT, when compared to the pre-treatment status [57–59].

Similarly, Chang et al. [57] also observed a smaller loss in cognitive function, assessed by HVLT, in learning and short term memory in patients with 1–3 BM treated with only brain SRT (which facilitated giving a lower radiation dose to

the hippocampus) as compared to those receiving WBRT. A study by Welzel et al. [59] used the AVLT test (Auditory Verbal Learning test) which reported lowered verbal memory already 6–8 weeks after completing WBRT in BM patients. In a phase III RTOG 0214 clinical study on patients with small cell lung cancer (at stage III clinical severity) undergoing prophylactic cranial irradiation (PCI), a clear reduction of cognitive function was observed at 3 months after brain RT when assessed by the MMSE test [60].

Cognitive disorders are also described in post-RT patients suffering nasopharyngeal carcinoma where, at approximately 5.5 years after radical RT, they exhibited memory and learning dysfunction compared to people of similar age but untreated with RT [61]. However, another prospective study on patients with nasopharyngeal carcinoma treated with RT by using Intensity Modulated Radiation Therapy (IMRT) found that, after 18 months post-RT, the test results of cognitive function in patients receiving an average dose exceeding 36 Gy to the temporal lobe were significantly different to those results prior the RT [62].

In summary, applying RT to the area around the brain affects cognitive function, which can already become apparent onwards from the second month after RT treatment, peaking at about 4 months post-RT [63] (Tab. I).

Cognitive impairment/dysfunction following brain RT

Around 90% of BM patients evince some loss of cognitive function even before starting RT whilst in two thirds cases there are further losses in cognitive function following brain RT [64]. This deficit/deficiency is caused not only by the presence of brain cancer itself, but also through the progressive effects of extracranial chemotherapy (CHT) or adjuvant therapy (including the use of opioids, steroids) as well as the presence of comorbidities or the natural deterioration of cognitive functions in elderly patients [65, 66].

A key factor for maintaining normal mental function in patients with brain tumour lesions is to prevent their progressing in the brain through, for example, the use of WBRT [65]. The search for alternatives to preserve or improve cognitive function, (for instance by pharmacological means), have not achieved the desired results; an example is afforded by the RTOG 0614 study that used memantine as a potential neuro-protecting agent during WBRT and which showed no effect on cognitive maintenance [67].

The most commonly reported deficits in cognitive function after brain RT is memory impairment; often short-term, sporadic-deferred [56, 57, 60, 68–70]. Ones less common are in remembering/recalling information and in learning [57, 68–70]. Those also reported include impaired verbal memory, necessary for understanding a read text [56, 59]. In addition, impaired fine motor function can be observed in the upper limbs and as well as in executive function;

the higher cognitive processes determining responses to new and difficult/challenging situations, such as initiating and halting a given response, planning or organising [56]. It should be stressed that the deterioration, to any extent, of each cognitive function after WBRT leads to a reduced QoL [85, 89].

The incidence of neoplastic lesions in the hippocampus region

As yet, it is unclear whether the therapeutic gain from sparing the hippocampus outweighs the risk of disease progression at this location. A study by Gondi et al. [71] on 371 out of 1133 BM patients diagnosed by post contrast MRIT1, observed that tumours located in the hippocampus region (i.e. the hippocampus including a surrounding 5mm margin) account for only up to 3% BM cases and occur in around 8.6% of patients with brain cancer progression, for which there were no metastases present within the hippocampus itself. Marsh et al. [72] demonstrated that the majority of metastases in the limbic system area occurs in patients with multiple BM (> 3). It is worth emphasising that the SVZ, in which the NSCs are located represents 2.23% of the whole brain volume [73]. It turns out that the risk of metastasis in the hippocampal area is approximately 0.5% for oligo-metastatic disease, i.e. up to 3 BM and approximately 1.5% in cases of multiple BM [73].

Metastasis in the SVZ more often occurs in patients with small cell lung carcinoma (at 2.7%) compared to patients with other cancers (0.84%), such as non-small cell lung cancer (0.82%) and breast cancer (1.3%) [73]. Preliminary results from most studies indicate that the therapeutic gain achieved when implementing hippocampal sparing procedures during brain RT, (i.e. contouring hippocampal TK images and with fusing/integrating CT images from MRI in planning RT with a small 5 mm margin), outweighs the potential risk of local failure [80, 86]. However, in the possible event of metastases appearing within the hippocampal area then SRT may be considered [71].

Technical means for providing hippocampal sparing during brain RT

Sparing the hippocampal region of the brain during RT poses a technical challenge in that highly specialised radiotherapy techniques need to be applied such as IMRT, which provides protective covering/shielding for one or both of the centrally located hippocampi according to the patient's clinical requirements (Table II).

Hippocampal sparing in patients with primary brain tumours

There is scant research on this issue. *Marsch et al.* [92, 93] have shown that for patients undergoing IMRT in the surroundings of the brain tumour, it is possible to reduce their

Table I. Impairment of cognitive function in patients after brain radiotherapy

Study, year	RT schedule	Number of patients	Observation time (months)	Cognitive function test and significant cognitive decline.
Sun et al., 2011 [60]	PCI 30Gy/15fr	163	3,6,12	HVLT, MMSE — Significant decrease ($p < 0.0001$) in immediate HVLT response after 3 and 6 months and deferred response decreased after 6 months
Wolfson et al., 2011 [90]	PCI 25Gy/10fr	131	6,12	HVLT, COWA — declining HVLT outcomes by 62% after 12 months
	PCI 36/18 fr	67		HVLT, COWA — declining HVLT outcomes by 85% after 12 months
	PCI 36/2xdaily/24fr	66		HVLT, COWA — declining HVLT outcomes by 89% after 12 months
Chang et al., 2009 [7]	WBRT + SRS 30Gy/12 fr	28	3.5	HVLT — declining deferred memory after 3 months
Welzel et al., 2008 [10]	WBRT 40Gy/20fr	16	1.2	AVLT — declining outcomes by 57% after 2 months.
	PCI 36Gy/18 fr	13		AVLT — declining outcomes by 44% after 2 months.
Meyers et al., 2004 [14]	WBRT 30Gy/10fr	208	12	HVLT, COWA — decreasing cognitive function in both by 48%

Table II. Selected studies where hippocampal sparing was adopted

Study, year	Hippocampal dose					
	Number of patients	RT	Technique	Fractioning	D max	D av
Gutierrez et al., 2007 [82]	10	WBRT	HT	15x2,15 Gy	–	5.86 Gy
Gondi et al., 2010 [40]	5	WBRT	HT	10x3 Gy	12.8 Gy	*5.5 Gy
			LINAC		15.3 Gy	*7.8 Gy
Hsu et al., 2010 [81]	10	WBRT + SIB	LINAC	15x2,15 Gy	–	5.23 Gy
Marsh et al., 2010 [91]	11	PCI		15x2 Gy	–	12.5 Gy
		WBRT	HT	14X 2.5 Gy	–	14.3 Gy
Marsh et al., 2011 [92]	12	PBRT	HT	–	–	–
van Kesteren et al., 2012 [42]	10	WBRT	LINAC 3D CRT	12x2.5 Gy	13.5 Gy	6 Gy
Nevelsky et al., 2013 [93]	10	WBRT	IMRT	10x3 Gy	14.35 Gy	–
Prokic et al., 2013 [83]	10	WBRT + FSRT	Rapid Arc	12x2.5 Gy + 2x 9 Gy	12.33 Gy	7.55 Gy
		WBRT + SIB		12x2.5 Gy + 12x4,5 Gy	15.82 Gy	9.8 Gy
Awad et al., 2013 [94]	30	WBRT + SIB	Rapid Arc	5–15 fr	32.2 Gy	20.4 Gy
Pokhrel et al., 2015 [95]	10	WBRT	VMAT	30Gy/10 fr	11.2 Gy	15.6 Gy
Kothavade et al., 2015 [96]	10	PBRT	HT		–	20Gy
			IMRT	54 Gy/30 fr	–	25 Gy
Oehlke et al., 2015 [97]	20	WBRT + SIB	VMAT	30 Gy/12 fr, SIB to 51 Gy	–	6.58 Gy
Kim et al., 2016 [98]	11	WBRT + SIB	HT	25–28Gy/10–14 fr, SIB to 48 Gy	–	13.65 Gy
Giaj Levra et al., 2016 [99]	10	WBRT + SIB	VMAT	20Gy + 40 Gy/5fr	10.5 Gy	7.7 Gy

dose by 56.8% in order to spare the hippocampus and yet conform to the IMRT plan as compared to when this organ is unprotected i.e. 15.8 Gy vs 36.6 Gy. It should be noted that the central location of primary brain tumours often prevents shielding both hippocampi, particularly those ones immediately adjacent to the hippocampus, or those reaching into the hippocampal area because of tumour swelling [74]. Given this situation, many workers suggest sparing whichever hippocampus is tumour-free [75, 76].

Hippocampal sparing is especially vital to those children where primary brain tumours are diagnosed much more frequently than for adults. In children with gliomas of different histological grade, who received RT via tomotherapy, 56% and 52.1% reductions were achieved respectively in the physical or biological average doses of ionizing radiation by Marsh et al. [77] when the hippocampus is treated as a critical organ in RT planning, as compared to situations where it is not spared.

Hippocampal sparing in patients irradiated electively or those with BM

Blomstrand et al. [78] demonstrated that a variety of RTs during WBRT given to children permitted different radiation doses to be administered to the hippocampus. They found that the average dose given to the hippocampus and SVZ was 88.3% of the planned total IMAT dose (i.e. Intensity Modulated Arc Therapy), 77.1% of the IMRT and 42.3% for IMPT (Intensity Modulated Proton Therapy). Tarnawski et al. [79] reported that it was possible to achieve a 45% dose reduction when using helical tomotherapy as well as IMRT when planning PCI for 10 patients suffering from small cell lung cancer, whilst still preserving the therapeutic radiation dose to the rest of brain. Similar findings were demonstrated by Gondi et al. [80] on five patients when WBRT (30Gy / 10fr) was prescribed using helical IMRT or tomotherapy, where dose levels were respectively reduced by 87% and 81% for the hippocampus. In instances of hippocampal avoidance, the therapeutic dose is still, in homogenous fashion, applied to the rest of the brain.

The lowest dose delivered to the hippocampus was achieved by Hsu et al. [81] on 10 patients with up to 3 single BMs, where SIB-VMAT (Simultaneous Integrated Boost — Volumetric-Modulated Arc Therapy) was used post-WBRT, so as to increase the radiotherapy dose delivered to the BMs. The hippocampus received less than 6 Gy (5.23 Gy \pm 0.23 Gy) with respect to conventional fractioning after 2 Gy, whilst maintaining the planned/proscribed dose to the rest of the brain. Likewise, Gutierrez et al. [82] demonstrated on 10 BM patients undergoing WBRT, that it was possible to reduce the hippocampal dose to an average total of around 5.8 Gy with single fraction doses being 0.39 Gy, based on fractioning 2 Gy. A study by Prokic et al. [83] reported slightly higher doses, when using VMAT-SIB in BM patients also undergoing WBRT, of respectively 7.55 \pm 0.62 Gy and 6.29 \pm 0.62 Gy at hippocampal margins of 5 and 10 mm with respect to a 2 Gy fractionation. Additionally, it was observed that the SIB-VMAT technique allowed doses delivered to the hippocampus to become reduced even in those patients with up to 8 multiple BMs.

The fractional dose (DF) and total dose (DC) have still not yet been unequivocally defined, which would enable limbic system function to be retained/continued. Gondi et al. [44] determined that the EQD2 (Biologically Equivalent Doses in 2 Gy Fractions), of greater than 7.3 Gy delivered to more than 40% by volume of both hippocampi results in impairment of deferred memory and problems in learning and remembering. A study by Gutierrez et al. [81] defined an acceptable DF of 0.39 Gy and DC of 5.8 Gy relative to the EQD2. Although there is no clinical data on any average dose suitable to the hippocampus, it is assumed that a DC exceeding 15.8 Gy – 24.9 Gy is sufficient for retaining cognitive function [84].

Based on the RTOG 0933 study, preliminary recommendations were proposed for dose tolerances to the hippocampus in BM patients which could deliver a survival longer than 6 months when using WBRT, i.e. the DC should not exceed 7.8 Gy and the dose to the entire hippocampus should not exceed 10 Gy, whilst the maximum dose should not rise above 15.3 Gy [85]. The study suggests the contouring of critical structures responsible for neurogenesis, i.e. the SVZ with a 5 mm margin of surrounding tissue. A contour atlas of the hippocampus can be found on the RTOG website [86].

It is finally worth mentioning about the search for objective methods for assessing cognitive impairment in patients with post-cerebral RT. In a proton MR spectroscopy study on patients that had undergone WBRT 4 months earlier, reduced concentrations of N-acetylaspartate were noted; this being a metabolite of nerve tissue from the hippocampal region [87]. Another study using MR spectroscopy found sub-acute radiation damage to nerve tissue after a month post-WBRT [88]. It seems likely that such studies will in the future provide a more accurate assessment of cognitive impairment in patients after brain RT as opposed to those subjective methods for assessing the hippocampus, (i.e. the cognitive studies).

Summary and conclusions

RT in patients with primary and metastatic brain tumours is still an important treatment, but it remains associated with certain cognitive dysfunctions. The hippocampus is one of the brain structures that are acutely sensitive to ionizing radiation, particularly the so-called active neurogenesis regions in which NSCs proliferate. Indeed, NSC function has been proved to assure that the limbic system operates normally; this being primarily responsible for cognitive function.

Radiation damage to the hippocampus may play a key role for decreasing patient QoL after brain RT through cognitive impairment. Shortcomings in these functions commonly include problems with learning, memory, (both short-term and deferred) and processing of information previously stored. A series of studies using subjective methods for assessing patient's cognitive functions, post-RT, by means of psychological tests such as 'mini-mental', AVLT, HVLT or COWA demonstrated a distinct loss of cognitive function already apparent at about 2–3 months after treatment. An objective test or marker capable of detecting damage to hippocampal structures is however still being sought for.

Further clinical trials are required, which would allow the best RT to be selected, thus allowing the hippocampus to be protected in a variety of specific clinical situations. It is also important to define patient groups who could tangibly benefit from hippocampal sparing when undergoing brain RT.

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