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Title:

Treatment of Brain Metastases in Lung Cancer: Strategies to Avoid/Reduce Late Complications of Whole Brain Radiation Therapy

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Opinion Paragraph

Brain metastases occur in 20-40% of lung cancer patients. The use of whole brain radiation therapy (WBRT) has been shown to ameliorate many neurological symptoms, facilitate corticosteroid reduction, enhance quality of life (QOL) and prolong survival. The acute and early delayed side effects of WBRT are generally mild and inconsequential whereas late complications are often progressive, irreversible and may have a profound effect on neurocognitive function and QOL. Nevertheless WBRT remains the cornerstone for treatment of multiple brain metastases due to its efficacy and the paucity of other treatment options. In avoidance of WBRT and its potential toxicity, patients of good performance status and ≤3 metastases may be reasonably treated with focal therapy alone (surgery or radiosurgery) without a compromise in survival. In patients with multiple brain metastases and those undergoing prophylactic cranial irradiation (PCI) established methods to mitigate the late complications of WBRT include; total dose observation, dose per fraction restrictions, and avoidance of concomitant chemotherapy. Current areas of active research which hold great potential for benefit include hippocampal sparing radiotherapy and the use of neuroprotective agents.

Introduction

More than 200,000 people are diagnosed with lung cancer each year in the United States [1] . A significant number of these patients will be burdened with cerebral metastases. Various population based, hospital based and autopsy based studies report the incidence of brain metastases in patients with lung cancer to be greater than in any other malignancies. One of the more robust studies, a population based study from the Metropolitan Detroit Area run from 1973 to 2001 revealed 11763 brain metastases in 59038 lung cancer patients – an incidence of 19.9% [2]. The rate is highest in small cell lung cancer (SCLC) with a Dutch population based study from 1986 to 1995 showing an incidence of 29.7% with SCLC and 12.6% with non-small cell lung cancer (NSCLC) [3].

In SCLC in the pre-prophylactic cranial irradiation (PCI) era, an 80% chance of central nervous system metastases was reported in survivors at 28 months [4]. Within the NSCLC group, brain metastases are more common with adenocarcinomas and large cell carcinomas compared to squamous cell carcinomas [5].

Furthermore, as in other cancers, the incidence of brain metastases is rising due to multiple factors including earlier detection, principally by use of MRI, and longer overall survival as a result of superior local and systemic treatments [6, 7].

Whole Brain Radiation Therapy

The most frequently used treatment in the management of multiple brain metastases is WBRT. The use of WBRT has been shown to improve many neurological symptoms, allow corticosteroid reduction, enhance quality of life (QOL) and prolong survival.

Untreated, patients with brain metastases have a dismal prognosis with an estimated median survival of only a month [8]. Corticosteroids and anticonvulsants offer symptomatic benefit but median survival with corticosteroids alone does not exceed 2 months [9, 8]. Non-randomised studies suggest WBRT increases median survival to 3-6 months [9, 8].

Despite its benefits, WBRT is ultimately a palliative measure and the modest doses used are effectively sub-therapeutic for eradication of clinically evident disease. Higher doses are limited by the risk of normal tissue morbidity and perceived futility in the presence of uncontrolled extracranial disease.

Complications of WBRT

The complications from WBRT have generally been divided into three categories, divided according to time – acute, early delayed and late delayed [10, 11].

Acute reactions, which are generally mild and inconsequential, occur during or within a few weeks of radiotherapy. They are often due to an exacerbation of peritumoural oedema and include fatigue, headache, nausea and alopecia. Early delayed reactions occur typically ≤ six months after radiotherapy and include somnolence syndrome, short-term memory loss and acute leukoencephalopathy. Late delayed complications after WBRT create the greatest concern in patients and physicians. The onset is usually > six months after radiotherapy, is generally irreversible, progressive and may be fatal [10, 11]. Such complications may include radionecrosis, vascular injury and demyelination. Neurocognitive impairment can result from any of these but may also be identified in the absence of radiographically visible anatomical injuries [12].

There is a wide spectrum of neurological impairments described from the most severe, overt dementia, through to variable decline in memory, mood, concentration, attention and executive function.

Radiation induced dementia is uncommon. DeAngelis et al reported on dementia in groups of patients cured of brain metastases and described an overall 1.9-5.1% rate of dementia post radiotherapy. The most at risk patients were those who received high fractional doses (>3Gy), had concurrent chemotherapy and survived ≥ one year [13]. Milder neurological impairment, however, is detectable in the majority of patients treated with radiotherapy and its prevalence increases with time [14, 12, 15].

Studies attempting to assess impairment in neurocognitive function (NCF) are often difficult to compare as numerous definitions of neurological impairment are used, function is measured at different time points and a variety of assessment techniques are employed, including patient self-reporting, clinician observation, Mini Mental State Examination (MMSE) or a battery of neurological tests [16, 15]. The MMSE has been most frequently used but its weaknesses are well documented [17]. Trials in the current era tend to use a battery of neurocognitive tests to better detect and

quantify neurocognitive impairment. QOL has not been extensively studied in patients with brain metastases despite the fact that neurocognitive impairment has a significant impact on QOL [18, 19].

A recent review set out to determine the average incidence, magnitude and time to occurrence of radiation induced neurocognitive decline following WBRT [20]. The authors concluded that neurocognitive decline peaked at four months post WBRT, severity was usually mild (only 8% ≥ grade 2 on the SOMA-LENT scale) and thereafter marginal improvements were seen in NCF before a late decline in a biphasic pattern. NCF was directly related to control of brain metastases, that is, patients with uncontrolled cerebral disease exhibited the worst neurocognitive impairment. This last finding has been supported by multiple studies [14, 21] and is one of many factors that creates uncertainty when evaluating the impact of radiotherapy on neurological function. Furthermore a significant proportion of patients have neurocognitive impairment at baseline even without brain metastases [16, 22, 23]. Neurocognitive deterioration may also be attributed to other oncological treatments including chemotherapy, hormonal therapy, neurosurgical intervention, anticonvulsants, corticosteroids and opiods [24-27]. Fatigue, depression and medical co-morbidities may also be contributing factors. Furthermore, the combination of these therapies and co-morbidities with radiotherapy increases the risk of neurocognitive impairment beyond that of radiotherapy alone [28, 29].

Mechanism of injury

The mechanism of radiation induced injury which leads to late effects in the brain is not clearly established and is almost certainly multifactorial. The classical hypothesis of clonogenic cell death of endothelial cells and glial cells cannot feasibly explain many of the changes identified with radiation induced injury – particularly neurocognitive impairment. The current popular hypothesis is that of a dynamic interplay between multiple cell types within the central nervous system which is ultimately responsible for clinical neurocognitive decline [30, 11, 31].

TREATMENT

Dose-Fractionation Reduction in Prophylactic Cranial Irradiation (PCI)

The role of PCI and its impact on NCF has been studied in phase III randomised trials in both SCLC [32, 22] and NSCLC [33]. Gregor et al found ongoing NCF decline at 6 months and 1 year in both the PCI and observation groups but no significant difference between the two [22]. Arrigada et al also found no significance difference in NCF impairment between the PCI and observation groups over 2 years [32]. The more recent study by Sun et al found a statistically significant greater decline in Hopkins Verbal Learning Test (HVTL) immediate recall and delayed recall at one year in the PCI arm, but with no change in MMSE, QOL or Activities of Daily Living Scores it is difficult to assess the clinical relevance, if any of this change [33].

Compared with therapeutic cranial irradiation (brain metastases present), PCI appears to be associated with milder/less frequent NCF decline. This may be partially attributable to the lower total doses or doses per fraction generally used. In patients treated with PCI on the PCI99-01 study, a randomised controlled trial (RCT) of 25Gy versus 36Gy for limited stage SCLC, the authors found deterioration over time with communication, weakness in legs, intellectual deficit and memory without difference between dose groups [34]. The RTOG 0212 trial examined the effect of PCI dose and fractionation on chronic neurotoxicity and QOL in 264 patients, of which 146 were co-enrolled in the PCI99-01 trial [35]. Unlike the PCI99-01 trial they used a battery of neurocognitive tests and revealed a significantly greater degree of neurocognitive deterioration with 36Gy compared to 25Gy (85-89% versus 62% at one year). Both higher dose and age were statistically significant factors for developing chronic neurotoxicity. Greater dose per fraction and the use of concomitant chemotherapy during PCI also appear to be associated with increased risk of neurotoxicity [36].

Impact of dose/fractionation schedules

A Cochrane review of WBRT dose fractionation schemes did not show a benefit in neurological function with altered fractionation regimes compared to standard doses of 30Gy/10#, 20Gy/4# or 20Gy/5#) [37]. Hypofractionated regimes, however, have proven hazardous with significant acute complications. Regimes of 15Gy in 2 fractions [38] and 10Gy in one fraction [39] have both recorded radiation induced deaths in the acute phase.

Hippocampal sparing radiotherapy

Mitotically active neural stem cells (NSC) are located in two sites within the brain, the subgranular zone (SGZ) located within the dentate gyrus, and the subventricular zone (SVZ) on the lateral aspect of the lateral ventricle. NSC within the SGZ give rise to new hippocampal cells which, throughout adult life, migrate into the granular cell layer of the hippocampus [40]. Dentate gyrus granule cells are thought to have a function in learning and memory, particularly spatial memory [41]. There exists significant preclinical evidence that radiation induced injury to the hippocampus correlates with neurocognitive decline. Furthermore, in rodents, it appears that the NSC in the SGZ of the hippocampi may be the sensitive targets responsible for this decline [42, 43].

The concept of hippocampal sparing radiotherapy arose on the basis of this preclinical research combined with the fact that neurocognitive deficits following radiotherapy correlate with hippocampal dependent functions of memory, learning and spatial processing. Sparing the hippocampus should be safe as it is seldom involved with metastases. Wan et al examined 2270 metastases in 488 patients showing a 1.1% involvement by metastases in either NSC regions [44]. Gondi et al have shown no hippocampal metastases of 1133 metastases in 371 patients, but reported metastases within 5mm of the hippocampus in 8.6% of patients [45]. This 5mm peri-hippocampal region is stipulated as the avoidance target in the RTOG contouring guidelines [46] (figure 1). Gondi et al, using the RTOG contouring guidelines to define the hippocampus, have shown a correlation between hippocampal dose and

neurocognitive impairment in patients with low grade glioma with a bilateral hippocampal D40% >7.3Gy correlated with memory impairment [47].

The RTOG have completed accrual on a phase II trial examining the impact of hippocampal sparing WBRT on neurocognition and QOL (RTOG 0933). Participants were treated to a dose of 30Gy/10# with Tomotherapy or IMRT with the protocol stipulating a hippocampal D100% of ≤ 9Gy with a maximum dose ≤ 16Gy. Accrual was reached and closed in July 2012 and its primary objectives are, as yet unreported. The investigators have published limited data demonstrating, for a prescribed dose of 30Gy/10#, that hippocampal dose can be reduced to a median of 5.5Gy using helical Tomotherapy or 7.8Gy using LINAC based IMRT [45]. Indeed these low dose levels may be required due to the exquisite sensitivity of the neural stem cells [48].

Whilst these techniques are interesting and may yield beneficial outcomes it seems implausible that NCF is entirely dependent on the hippocampal function alone. In fact some propose that both NSC populations (SGZ and SVZ) or the entire limbic circuit should be spared and have shown that it can feasibly be performed [49-51].

Insert figure here

Fig.1 Right hippocampus with 5mm PTV margin contoured on axial, coronal and sagittal MRI images according to the RTOG 0933 Protocol [46]

Surgery or Radiosurgery alone (withholding WBRT)

There is limited role for local therapy in patients with diffuse cerebral metastases beyond surgical management of a dominant symptomatic lesion. In patients with limited cranial metastases however there has been significant interest in finding a group who may benefit from local therapy alone thus avoiding any potential WBRT related toxicity [52]. RCT have suggested that local therapy alone (SRS or surgery) for ≤ three brain metastases whilst associated with poorer intracranial control of disease, does not compromise overall survival [53-56]. These studies also assessed neurological, neurocognitive or functional endpoints.

Aoyama et al reported on a phase III RCT of 132 patients with ≤ four brain metastases randomised to SRS alone or SRS with WBRT (30Gy in 10 fractions) [53]. The primary endpoint was median survival and included amongst the secondary endpoints were KPS at one year, incidence of neurological death and MMSE score - none of which was significantly different between the arms.

Chang et al have published the only phase III RCT of SRS alone versus SRS plus WBRT (30Gy in 12 fractions) with NCF as the primary endpoint [54]. NCF was assessed with a battery of tests. The study was closed early after accrual of 58 patients when the data monitoring committee found a significant decline in HVLT-R measured learning and memory function at 4 months in the SRS plus WBRT arm (52%) versus the SRS alone arm (24%). Strikingly the survival was significantly longer in the SRS alone arm (15.2 months versus 5.7 months; p=0.003), despite a higher rate of CNS recurrence at one year (73% versus 27%; p=0.0003). The authors

concluded that the study provided "Level 1 evidence to support the use of SRS alone in the initial management of patients newly diagnosed with one to three brain metastases".

The validity of that conclusion was considered somewhat controversial, and drew criticism from observers [57, 58] who cited methodological flaws and inconsistencies with the results of other RCT showing equivalent survival in those receiving WBRT [53, 55, 56].

The European Organisation for Research and Treatment of Cancer (EORTC) compared 359 patients of WHO performance status (PS) 0-2 with ≤ three brain metastases in a phase III RCT of local therapy (surgery or SRS) alone or in combination with WBRT (30Gy in 10 fractions) [55]. Overall survival and median time to WHO PS > 2 were similar in both arms. Salvage therapies were used more often in the observation arm and intracranial progression as a cause of death was more frequent in the observation arm (44%) than in the WBRT arm (28%). No dedicated NCF testing was performed but Health Related Quality of Life (HRQOL) was a secondary endpoint. In summary patients in the observation arm scored higher HRQOL scores with significant differences found in a few, transitory areas (fatigue and physical functioning at 8 weeks, global health status at 9 months and cognitive functioning at 12 months) [59]. The authors' conclusion was that observation after surgery/SRS and close monitoring with MRI is reasonable in well-performing patients with stable systemic disease and ≤3 brain metastases, and is not detrimental to HRQOL.

This remains a controversial area particularly as intracranial control, which is where the addition of WBRT is most effective, has been shown to correlate with maintenance of NCF and QOL [14, 60, 21]. On balance however it appears reasonable to consider SRS alone and close monitoring for patients with ≤ 3 brain metastases.

Neuroprotectors

Memantine

Vascular injury following radiation therapy is well recognised [30, 11] and its pathogenesis has similar mechanisms to those underlying vascular dementia [61]. Medications that have proven beneficial in improving neurocognitive function in vascular dementia have thus been considered for a role in preventing neurocognitive impairment following cerebral irradiation.

Memantine is a N-methyl-D-aspartate (NMDA) receptor antagonist with proven efficacy in vascular and Alzheimer's dementia [62]. Under basal conditions the neurotransmitter glutamate binds with the NMDA receptor and through this action is involved with synaptic plasticity and consequentially memory [63]. Following ischaemic insults, an increase in glutamate levels can rapidly occur giving rise to a 'gluatamatergic storm' which causes excessive NMDA receptor stimulation and subsequent cell death (excitotoxicity).

The RTOG examined the potential of memantine in preventing cognitive dysfunction in patients receiving WBRT in a RCT - RTOG 0614. This is yet to be published but was presented in abstract form at ASTRO 2012 [64]. Patients received WBRT (37.5Gy in 15 fractions) and were randomised to receive placebo or memantine, 20mg/day, within three days of initiating radiation therapy, for 24 weeks. The primary endpoint was memory decline as measured with the HVLT-R Delayed Recall (HVLT-R DL) at 24 weeks. 554 patients were accrued of whom 508 were eligible. When comparing patients in the two arms, patient and treatment characteristics were well balanced and study compliance was similar. Only 32% of the patients completed the drug therapy per protocol mainly due to a poorer than expected survival and progressive disease which led to non-compliance. No differences in overall survival or progression free survival were seen between the arms. Concerning the primary endpoint, there was less decline on the HVLT-R DR in the memantine arm (median decline of 0) compared to the placebo arm (median decline of -2) at 24 weeks (p=0.059). Although this was not statistically significant, memantine was shown to delay time to cognitive decline (p=0.02) and patients in the memantine arm experienced a 17% relative reduction in cognitive decline at 24 weeks compared to those in the placebo group (p=0.01). The final publication is eagerly awaited before a conclusive recommendation can be made regarding the use of memantine after WBRT for brain metastases.

Donepezil

Donepezil, an acetyl cholinesterase inhibitor, is used to treat mild to moderate dementia in Alzheimer's disease. Donepezil delays the breakdown of acetylcholine in synaptic clefts and by doing so enhances cholinergic neurotransmission, which is associated with memory. Donepezil administration for 24 weeks, in a group of patients with primary brain tumours who had survived ≥6 months post radiation, was shown to improve cognitive function, mood and health related QOL [65]. Based on these positive findings a randomised phase III, placebo controlled, double blinded trial of donepezil and partial or whole brain radiotherapy was conducted, completed and presented in abstract form at ASCO 2013 [66].

In this study 198 adult survivors of primary and metastatic brain tumours, who completed cerebral irradiation to ≥30Gy at least 6 months prior to enrolment, were randomly assigned to receive 24 weeks of Donepezil 5-10mg per day or placebo. Cognitive function was assessed at baseline, 12 and 24 weeks with a battery of neuropsychological tests with a Cognitive Composite (CC) score as the primary outcome. 74% of participants completed the study. The CC score improved significantly by 24 weeks in both arms (p<0.01) however, there was not a statistically significant difference between the groups (p=0.57). The donepezil group performed better than placebo on HVLT Recognition (p=0.03), Discrimination (p=0.01) and GP-Dominant Hand (p=0.02). Statistically significant interactions were found between the treatment arm and baseline cognitive scores for several test components and in all cases the benefit of Donepezil, relative to placebo, was greater for those with worse baseline scores. The authors concluded that there may be a role for donepezil in the treatment of long-term cerebral radiotherapy survivors who have cognitive impairment, particularly in verbal memory, working memory, visuomotor and psychomotor performance and executive functioning. The final publication is awaited.

The appeal of pharmaceutical agents that can recover lost neurocognitive function is attractive in that it avoids the potential toxicity and side effects of taking a mitigating agent in patients who are destined to early relapse and short survival, where neurocognitive decline may not become a concern.

Lithium

Lithium carbonate is used as a mood stabiliser primarily in the treatment of bipolar disorder. Recently it has been shown to have neuroprotective effects with regard to a wide range of cerebral insults including ischaemia, neurodegeneration, neuroinflammation and radiation [67-70]. Patients with bipolar disorder treated with lithium for 4 weeks show an increase in brain grey matter and hippocampal volume as identified on MRI imaging [71]. Various animal studies have demonstrated the positive effect of lithium on the hippocampus, including rodent studies which have shown that under normal conditions, without cerebral insult, lithium administration can enhance hippocampal neurogenesis [72], and that lithium protects irradiated hippocampal neural progenitor cells from apoptosis, translating to improved cognitive performance [73, 69]. It is reasonable to hypothesise that the neuroprotective benefits seen in ameliorating the cognitive loss with irradiation in animal studies may translate to benefits in humans.

The direct mechanism of lithium's neuroprotection is unclear, but potentially its major neuroprotective actions come from its inhibition of glycogen synthase kinase 3 beta, activation of Akt, suppression of p53 and Bax expression and increase in Bcl-2 expression [69].

Our institution is involved in a feasibility study of lithium use with prophylactic cranial irradiation for patients with small cell lung cancer. Radiotherapy will be prescribed at 25Gy in 10 fractions and patients will be randomised to receive either lithium (at a blood plasma range of 0.4 to 0.8mmol/L, 1000-2500mg/day) or placebo. Lithium will be administered for 6 weeks commencing one week after the end of radiotherapy. Cognitive impairment will be assessed via a battery of neurocognitive tests. The study feasibility will be measured by successful accrual, safety and randomisation tolerability [74].

Renin Angiotensin System (RAS) Blockers

The RAS is recognised as having localised effects within organs as well as its systemic role in blood pressure and fluid balance regulation. The local brain RAS system is complex and involved in blood pressure regulation, fluid and food intake, temperature regulation, motor control, maintenance of the blood brain barrier, learning, memory, behaviour and emotions [75]. RAS may be involved with the chain of events leading to radiation induced injury as blockade of the RAS in irradiated rats has been shown to have mitigating effects on radiation injury in both kidney and lung [76, 77].

Pharmacological agents available that interrupt the RAS at different points include Angiotensin Converting Enzyme Inhibitors (ACEI) and Angiotensin II type 1 receptor Blockers (ARB). RAS blockers are attractive drugs for translational clinical trials as they are commonly used, have an established side effect profile, are well tolerated, show positive results in preclinical trials and might enhance cancer therapies [78, 79]. The first proof of benefit was shown by Kim et al who administered ramipril for six months to rats treated stereotactically to the brain with 30Gy. Using a well-characterised optic neuropathy model the authors showed profound reduction in the demyelination of optic nerves and reduced severity of visual injury with chronic ramipril usage [80]. The administration of the ARB L-158,809 to rats 3 days prior through to 5, 26 or 52 weeks after WBRT to 40Gy (2 x 5Gy per week for four weeks) prevented or ameliorated radiation induced cognitive impairment [81].

Although both ACEI and ARB have demonstrated activity in modulating radiation induced brain injury, the exact mechanism of their action is not well understood. The initial presumption that RAS blockers worked through a reduction in neuroinflammation appears inadequate or incomplete. Conner et al administered L-158,809 to rats before and after a single 10Gy fraction to the brain. Despite reducing cognitive deficits there was no reduction in the neuroinflammatory microglial response or impairment of neurogenesis [82]. This is in contrast to the results reported by Lee et al who administered ramipril to rats before and after fractionated WBRT and noted a reduction in microglial activation in the dentate gyrus [83]. Radiation induced impairment of dentate gyrus neurogenesis was mitigated following administration of atorvastatin (a statin) and ramipril in combination, before and after WBRT [84]. Other possible mechanisms of action of RAS blockers involve an alteration in the balance from angiotensin II to Angiotensin-(1-7), which limits inflammation and oxidative stress, and inhibition of nicotinamide adenosine dinucleotide phosphate oxidase-mediated oxidative stress inflammation [79].

Perioxisomal proliferator-activated receptor (PPAR) agonists

PPAR agonists are ligand activated transcription factors of the nuclear hormone receptor superfamily. PPAR agonists have been trialled successfully in several CNS injuries and diseases to decrease neuroinflammation with the goal of limiting injury [85]. Fenofibrate, a PPARα agonist, is used as a cholesterol lowering agent often in combination with a statin. Ramanan et al studied the impact of fenofibrate on preserving hippocampal neurogenesis in mice after WBRT and found that the PPARα agonist both preserved hippocampal neurogenesis and inhibited microglial activation [86]. A subsequent study, however, on the PPARδ agonist GW0742 administered to mice irradiated with a single 10Gy WBRT dose prevented an increase in inflammatory markers and hippocampal microglial activation but did not rescue neurogenesis or prevent early delayed hippocampal dependent neurocognitive impairment [87]. Pioglitazone, a PPARγ agonist, administered before, during and post radiation prevented radiation-induced cognitive impairment in young adult male rats, but starting Pioglitazone after radiation did not significantly reduce radiation-induced cognitive impairment [88].

These studies suggest that PPAR agonists may ameliorate radiation induced cognitive impairment and may do so independent of any impact on neurogenesis. Researchers

at Wake Forest Baptist Medical Centre have championed the investigation into PPAR agonists and a clinical phase I/II study of pioglitazone for the prevention of radiation induced cognitive dysfunction is currently recruiting [89].

Other Investigational Agents

Many other agents have been or are currently being investigated for potential activity in reducing the impact of cerebral irradiation on neurocognitive function. Some of the more recent publications have explored the use of fingolimod [90]; estrogens [91]; minocycline [92]; baicalein [93]; statins [84]; ginkgo biloba [94]; hesperidin [95]; dragons blood (the plant resin Dracaena cochinchinensis) [96] and tamoxifen [97].

Perhaps one of the most intriguing findings was by Wong-Goodrich et al who found that daily running (by introducing a running wheel into the rat cage) following WBI prevented the marked decline in spatial memory retention observed months after irradiation [98]. Their findings suggest exercise may have a role in ameliorating radiation induced cognitive decline.

Neural Stem cell Transplantation

The promise of renewal by stem cell transplantation has been explored. Transplantation of human embryonic stem cells into the hippocampal formation of athymic nude rats 2 days after cranial irradiation (10Gy) ameliorated radiation induced hippocampal dependent cognitive impairment at four months. In addition, significant stem cell survival was found at 1 and 4 months post-irradiation and transplanted cells showed migration to the SGZ and signs of neuronal differentiation [99]. While these findings suggest further investigation is warranted there are multiple complex scientific and ethical issues to navigate before this technology will enter the clinical arena [100].

Conflict of Interest

Mark G. Shaw declares that he has no conflict of interest.

David L. Ball has board membership with Boehringer-Ingelheim, Pfizer, and Lilly Oncology and received payment for the development of educational presentations from Lilly Oncology and Pfizer.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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have been highlighted as:

- • Of importance
- •• Of major importance

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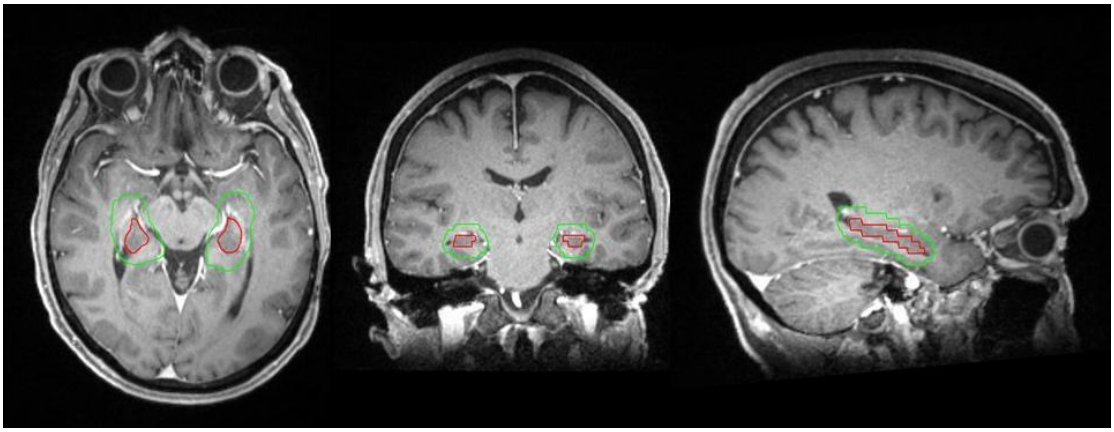

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