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Systematic Review

Effects of brain radiotherapy on cognitive performance in adult low-grade glioma patients: A systematic review

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ABSTRACT

Grade II gliomas are slow growing tumours that usually affect younger patients. The mainstream treatment modality at present is surgical. The role of radiation therapy in the management of grade II gliomas has been the subject of considerable debate. Radiation therapy has a proven potential to prolong progression free and overall survival in high-risk patients, but may also produce long-term cognitive deficits. Since grade II glioma patients are expected to live several years, retention of cognitive capacity and quality of life is an equally important endpoint as prolonging progression free survival. Our overarching goal is to critically review the available evidence on the possible neuropsychological effects of postoperative radiotherapy in adult grade II glioma patients. We performed a systematic literature search in Medline, Embase and Cochrane databases up to 1st of May 2020 for studies assessing the cognitive effects of radiation therapy on grade II glioma patients. Eleven studies meeting our inclusion criteria provide either negative or contradictory data regarding the cognitive domains affected, while major confounding variables remain incompletely addressed. The available evidence does not adequately support the notion that current radiation therapy protocols independently produce substantial cognitive decline in grade II glioma patients and therefore it would be premature to argue that radiation associated cognitive morbidity outweighs the benefit of prolonged survival. A large prospective study incorporating a full battery of neuropsychological testing, sufficiently long-term follow-up period and tight control of confounders is due to provide high quality data.

Grade II gliomas (LGG) are primary slow growing brain tumors deriving from glial cells and comprising approximately 15% of all primary brain tumors. They tend to affect younger people, usually before the age of 50 and allow an estimated average survival of 8–15 years [1,2]. Grade I gliomas affect mainly children and are frequently curable, in case a complete excision has been achieved. Unfortunately, grade II gliomas are known to transform to higher grade tumors [3,4]. To date, there is still considerable debate regarding the optimal treatment modality strategy. In the recent past, a watch and wait approach was acceptable [5]. However, new evidence indicates that a more aggressive approach, involving supramarginal (beyond the FLAIR signal margins) resection or even staged surgical resection, correlates with longer overall survival [1,2,6]. Apart from surgery, which is the basic treatment option for grade II gliomas, the optimal use of radiotherapy is under considerable debate.

Several influential studies have addressed the relevant issues and are guiding current clinical practice. These efforts documented that certain characteristics of grade II glioma patients such as older age (>40 years old), incomplete surgical resection, large preoperative tumor size (>4 cm), tumors crossing the midline, and adverse tissue molecular characteristics (eg IDH wild type and lack of 1p/19q co-deletion) signified poorer prognosis [7,8]. Postoperative management, thus, entails employing these risk factors [9–11] to stratify LGG patients either as high risk—who receive adjuvant radiotherapy and chemotherapy in the immediate postoperative period—or as low risk—who are closely monitored and receive adjuvant therapy when clinical or radiological disease progression is manifested [12].

The EORTC trial 22845 [13] elegantly described the therapeutic limitations of radiation therapy in LGG patients; it can slightly prolong the progression free survival, but fails to produce significant increase in overall survival. As we are approaching a stage where grade II gliomas can be viewed as a chronic disease, concerns over radiation-associated morbidity become even more relevant. The dose limiting morbidity of radiotherapy for CNS is late radiation

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injury which can manifest either as focal injury (presenting with mass effect) or as diffuse insult (presenting with cognitive decline; [14]. This later complication is a familiar and feared complication in pediatric patients [15–17] but can affect adults as well, especially younger ones [18]. Irradiation produces brain injury by a complex interplay of several mechanisms. Radiation inflicts microvasculature changes akin to small vessel disease producing ischemia and rise in extracellular glutamate [19]. Endothelial damage disrupts the blood brain barrier, introduces inflammatory processes and sustains a toxic microenvironment in the irradiated brain [20]. Chronic inflammation is furtherly sustained by microglial proliferation and activation [21]. Additionally, radiation induced senescence is a result of double strand DNA breaks (directly or via reactive oxygen species). The senescence-associated secretory phenotype of irradiated astrocytes meditates chronic inflammation and induces neuronal apoptosis [22,23]. Moreover, irradiation impairs neurogenesis and suppresses the differentiation of neural progenitor cells in the dentate gyrus, subgranular zone of the hippocampus and the subventricular zone of the lateral ventricles [24] and hence irradiation of the hippocampus has been associated with long term cognitive effects [25,26].

Cognitive decline is correlated to specific structural cerebral changes, namely cerebral atrophy and white matter changes. The magnitude of these changes is clearly related to the radiation-associated cognitive decline [27]. Conventional diagnostic imaging can show the reduction in hippocampal volume [28]and a dose dependent reduction in cortical thickness [29]. DTI studies are exceptionally sensitive in detecting white matter changes, which are most apparent in the fornix, cingulum and corpus callosum [30] while spectroscopy can detect radiation associated molecular irregularities (eg a decrease in N-Acetylaspartate/Creatinine & Choline/creatinine ratios) even in apparently normal parenchyma [31].

In light of this and of the fact that large radiation fractions failed to produce superior outcomes both in the NCCTG/RTOG/ECOG trial [32] and the EORTC 22844 trial [33], low dosage focal radiotherapy with fractions <2 cGy became the standard of care [34]. Interestingly, the EORTC 22033-26033 trial [11] and Wahl et al [35] examined the case for immediate chemotherapy and delayed radiation therapy compared to upfront radiation therapy. No difference in progression free survival was documented except in the IDH-mutant & non 1p/19q co-deleted subgroup, where RT prolonged PFS.

Since LGG patients tend to be young, traditionally used end points, such as tumor reoccurrence or overall survival, need to be carefully balanced against cognitive and behavioral aspects which are crucial for the functioning of an individual with a chronic disease. In other words, the patient would be expected to function at a high level in society for as much as possible and for as long as possible. Preservation of higher cognitive functions becomes a vital end point, equally important to the length of survival. As any treatment modality needs to carefully balance its therapeutic effect versus its toxicity, the cognitive effect of focal low fraction RT will eventually determine its role in the management of grade II gliomas In this context, the effects of radiotherapy (RT) in the management becomes very relevant and there is an ongoing debate regarding its use, benefits and side effects. The aim of the present systematic review is to assess the effects of radiotherapy on cognition in patients with grade II gliomas. This subject is presently particularly relevant as there is a phase III trial recruiting patients (1608-EORTC-BTG [I-WOT]) with the aim to investigate whether early post - operative radiotherapy of IDH mutated 1p/19q intact astrocytoma patients combined with chemotherapy would improve outcome and would outweigh potential complications including those of neurocognition/ quality of life.

Methods

The present systematic review was conducted in accordance with the PRISMA guidelines [36]. We searched the Medline, Embase and Cochrane databases for all relevant literature published in English up until 1st May 2020. The literature search strategy used is provided in Table 1a.

The main inclusion criterion was adult patients with grade II gliomas (astrocytomas or oligodendrogliomas). Pediatric studies and studies including patients with high grade gliomas, metastases, optic nerve gliomas or infratentorial tumors were excluded. The patients may have received any radiotherapeutic regime (e.g. photon based RT, 3D conformal RT, proton beam therapy, stereotactic radiosurgery, intensity modulation radiotherapy or brachytherapy). To avoid the potential confounding effect of chemotherapeutic agents, studies in which patients received both chemotherapy and radiotherapy were excluded. The included studies also evaluated the cognitive performance of the treated patients in the form of neurocognitive battery and offer a comparison with either a control group of grade II glioma patients receiving no radiotherapy or with the baseline performance of the patients themselves before starting radiation therapy. Table 1b summarizes the inclusion criteria in terms of PICOS.

The search yielded in total 3241 results; removal of duplicate entries yielded 2637 remaining articles (Fig. 1). Seventy-one articles were deemed appropriate for full text review. In total 61 were excluded; 20 because of no extractable data, 28 studies did not have an appropriate patient sample, 17 employed inappropriate intervention and 9 were inappropriate study type (Fig. 1). Articles may have been excluded for multiple reasons; hence they can fit in two or even three exclusion categories.

Results

Eleven articles providing data for 10 studies (5 of them being retrospective and 5 prospective) met our inclusion criteria. Nine studies offered data for 678 patients; one study [37] provided the long term outcomes of patients examined in an earlier study [38] and one study has its results reported in two articles [39,40]. Three papers [38,41,42] provided a comparison between 147 grade II glioma patients receiving radiotherapy and 132 patients with no radiotherapy. In seven studies the patients served

Table 1a
Search strategy employed for identifying relevant literature.

Search terms	(astrocytoma or glioma or oligodendroglioma or astrocytic or oligodendroglial) and (radiotherapy or radiation or cranial irradiation or irradiation or XRT) and (cognition or cognitive or dementia or functional or emotion or psychological or emotional or memory or mental or mental disorders or attention or mood)

Table 1b
PICOS inclusion and exclusion criteria.

	Inclusion Criteria	Exclusion Criteria
Patients	Patients of any age with hemispheric diffuse grade II gliomas (astrocytomas, oligodentrogliomas).	High grade gliomas, metastases, optic nerve gliomas, infratentorial tumors
Intervention	Any radiotherapeutic treatment. (Intensity-modulated radiation therapy – IMRT), (Stereotactic-radiosurgery), (Three-Dimensional conformal radiation therapy – 3D-CRT) (Brachytherapy), (Proton Beam Therapy), (photon based RT)	Patients receiving both chemo- and radiotherapy
Comparisons	Patients receiving radiotherapy VS patients not-receiving radiotherapy or none	
Outcomes	Primary outcome measures: Effect of treatment on cognitive function	
Study Design	Randomized controlled trials, Non-randomized controlled trials, retrospective, prospective, concurrent cohort studies, at least10 patients. Published in English	Expert Opinions, Comments, letters to the editor, case reports, animal studies, conference reports, studies with no outcomes reported, reviews

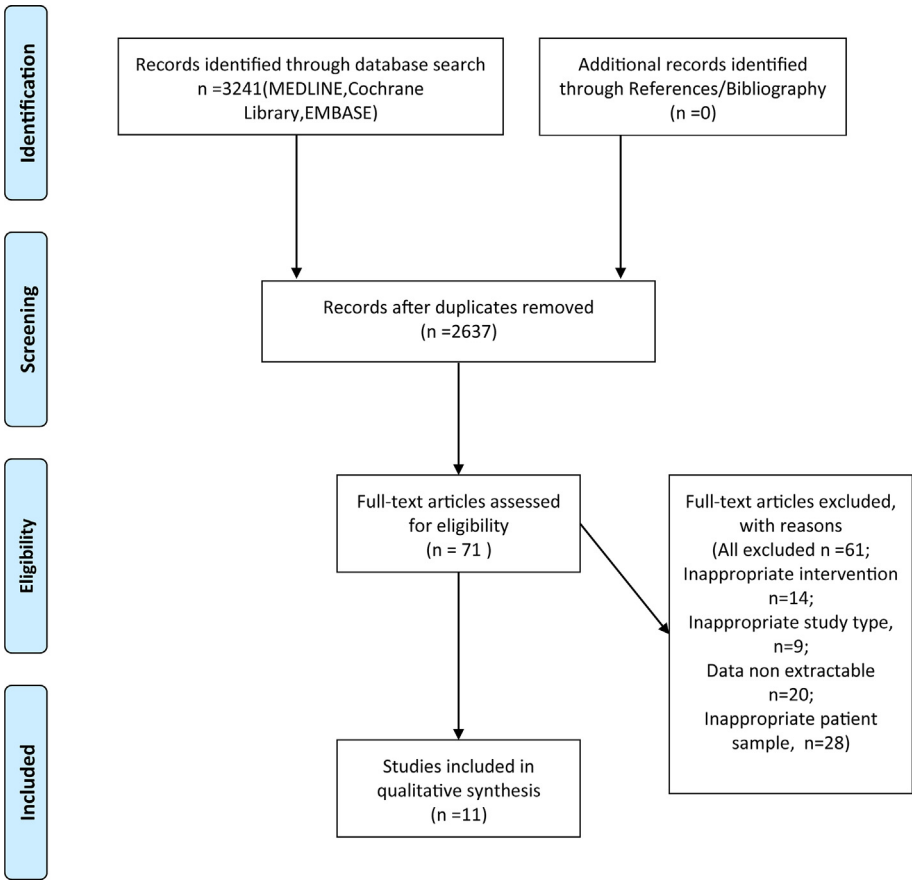

Fig. 1. PRISMA flow chart illustrating the search strategy.

as their own controls, as a baseline performance was obtained prior to RT treatment and then follow up post-RT assessments were scheduled. Nine articles assessed the modality of fractional focal radiotherapy in the treatment of grade II glioma patients while the remaining two actually reported on a single study employing proton beam therapy. The radiation doses ranged between 45 and 64 cGy provided in fractions of 1.8–2.6 cGy (Table 2).

The included studies evaluated neurocognitive performance employing diverse measures of varying and inconsistent depth. Brown et al. [43] used the basic cognitive evaluation provided by the mini mental state examination in a large sample, while others, like Sherman et al. [40] employed a more comprehensive battery of cognitive tests assessing individual cognitive domains. General cognitive function was assessed with either the MMSE or full cale IQ tests. Mini Mental Examination is a fast cognitive screening measure proposed by Folstein et al. [44] for dementia assessment which includes quick evaluation of orientation to place and time, memory, executive functions, aphasia and apraxia.

Four prospective studies [43,45–47] employed MMSE to monitor the cognitive function of 376 LGG patients receiving RT for a follow up period ranging between 3 and 5 years. None of these three studies noted statistically significant changes in the MMSE at any point of the follow up period. Surprisingly, patients with

Table 2a
Summary of included studies.

Author	Study type	Sample	Tumor type	Intervention	Intervention Dose/Duration	Neurocognitive examination time
Yavas et al. 2011	Prospective study	43 pts, >18 yo (median 36 yo), No control	LGG (4 Grade I, 35 Grade II; oligodendroglioma, astrocytoma, oligoastrocytoma), 4 not LG	Conformal external beam radiotherapy	Total dose 54 Gy in 2 Gy daily fractions	Baseline, 3rd, 6th, 12th, 18th, 24th, 30th, 36th mos
Taphoorn et al. 1994	Case-control Retrospective Study	35/41 hemispheric LGG [two groups with LGGs cases (17/20 pts had hemıspheric LGG RT+, 18/21 pts had hemispheric LGG RT−)], One control group (19 pts 35–71 yo with mean age 53.3 ys) with NHL/CLL	LGG (astrocytomas & oligodendrogliomas)	External beam radiation, 4–6 MeV photons	Total dose ranged from 45 to 63 Gy; the number of fractions (1.8–2.0 Gy) varied between 25 and 35, given in 30 to 55 days	Neuropsychological/QoL assessment to long term LGG survivors, surgery/RT took place at least one year ago, mean interval between histological diagnosis and test was 3.5 ys
Taphoorn et al. 1992	Retrospective study	11 pts (11/12 neuropsychologically assessed), 26–66 yo	5 oligodendrogliomas (4/5 were able to participate in cognitive tests), 7 astrocytomas)	Focal brain radiotherapy (4 or 6 MeV photons)	Total dose ranged from 4500 to 6120 cGy; the number of fractions varied between 25 and 34, given in 30 and 54 days	NM exactly; the enrolled pts had surgery/RT at least one year previously
Surma-aho et al. 2001	Retrospective cohort study	49/51 pts (26 LGG/RT+, 23 LGG/RT−) *2 pts from LGG/RT + group excluded as they received both radio + chemo*	11/23 LGG/RT – Gr I, all LGG/RT +Gr II	Whole brain radiotherapy (WBRT) (17 pts), Focal brain radiotherapy (FBRT) (9 pts)	WBRT; 40 Gy from two opposing fields, and a 20 to 28 Gy booster to the tumor bed FBRT; median total dose of 60 Gy (range, 56–66) in 28–34 fractions.	Mean follow-up of 7 ys for the RT+ group and 10 ys for the RT− group
Shih et al. 2015	Prospective study	20 pts, 22–56 yo (mean age 37.5 yo). No control	WHO GrII LGGs (7 astrocytomas, 4 oligodendrogliomas, 9 oligoastrocytomas)	Fractionated proton therapy	Total dose 54 Gy at 1.8 Gy per fraction over 6 wks.	Baseline (= within 8 wks of initiating RT), 3, 6, 12, 24, 36, 48 & 60 mo after the completion of RT. Median follow-up at data cut-off time was 3.2 ys for progressed pts (11/20) and 5.1 ys for stable ones (9/20)
Sherman et al. 2016	Prospective study	20 pts, 22–56 yo (mean age 37.5 yo)	WHO GrII LGGs (7 astrocytomas, 4 oligodendrogliomas, 9 oligoastrocytomas), 12 right hemisphere, 8 left (no control some full some partial others no resection	Fractionated proton therapy	Total dose 54 Gy at 1.8 Gy per fraction over 6 wks	Baseline (=within 8 wks of initiating RT), 3, 6, 12, 24, 36, 48 and 60 mo after the completion of RT. Median follow-up at data cut-off time was 4.9 ys for progressed pts (8/17 alive) and 5.1 ys for stable ones (9/17 alive)
Laack et al. 2005	Prospective study	20 pts, 9 pts 18–40 yo and 11 pts >40 yo, no controls	LGGs GrI or II; 2 astrocytomas, 9 oligodendrogliomas, 9 oligoastrocytomas	Focal Radiotherapy	Low dose group'; Total dose 50.4 Gy in 28 fractions of 1.8 Gy 'High dose group'; Total dose 64.8 Gy (extra 14.4 Gy boost dose)	Baseline (before RT), at 18 mos intervals for 59 mos after completing RT (mean follow-up 3 ys, every pt underwent at least two evaluations)
Brown et al. 2003	Prospective randomized clinical trial	203 pts >18 yo with LGG; 187 pts had baseline neurocognitive assessment, 101 pts who were still alive, had median follow-up 7.4 ys. No controls	LGG WHO GrII (astrocytomas, oligodendrogliomas, oligoastrocytomas)	Focal conventional/conformal Radiotherapy	Lower-arm dose group'; Total dose 50.4 Gy in 28 fractions 'Higher-arm dose group'; Total dose 64.8 Gy (extra 14.4 Gy to the preoperative tumor volume in 8 fractions)	Baseline, 1, 2, 5 yrs after radiotherapy
Douw et al. 09	Retrospective study	65 (no controls)	LGG (astocytoma 72%, oligodendroglioma 12%, oligoastocytoma 9%)	Focal Radiotherapy	<2Gy per dose (29/32). Mean 56.6 Gy, sd 7, mean 30.6 fractions of 16–2.5 Gy per fraction.	1st and second assessment (33 no RT, 32 RT) at 12 sd 3.9 range 6–28
Klein et al. 2002	Retrospective study	195 (91 of them, control group)	LGG (73 astrocytoma, 24 oligo dentrogliomas 7 oligoastrocytoma)	Focal Radiotherapy	55.6+ −6.1, fraction 2 (18% >2 gy fraction)	Testing 1 year post primary treatment with no recurrence within the last 3 months
Prabhu et al. 2014	Prospective study	126 RT (no control, 125 received RT & PCVl)	LGG (23 astrocytoma, 4 oligodentroglioma, 32 mixed astrocytoma/oligodendroglioma)	Focal Radiotherapy	54 Gy, 30 fractions of 1.8 Gy over 6 weeks	Baseline, 1, 2, 3, 5 ys

Table 2b
Summary of Included studies (continued).

Author	Cognitive functions studied	Primary outcome (Cognitive function)
Yavas et al. 2011	MMSE, EORTC QLQ-C30 (contains one cognitive domain)	Among MMSE scores, the only factor that was significantly different (increased) during follow-up period was recall score. Pts taking anti-epileptic drugs had lower cognitive function in 3rd year of follow-up
Taphoorn et al. 1994	Stroop Color word test; **language & executive functions,** Wechler Intelligence Scale for Children (WISC); **planning & foresight,** Rey-Auditory Verbal Learning Test (AVLT); **global memory & specifically verbal functions**, Categoric fluency task, Concentration endurance test (d2-test); **sustained attention in series of speed & connectness**, Benton Facial Recognition & Judgment of Line Orientation; **Non-verbal (right hemispheric) processes evaluation** tests	LGG/RT+ & LGG/RT− groups did not differ significantly in any of Neuropsychological assessment scores. Only pts with left hemisphere LGGs yielded a significant difference in the speed scores of the Stroop word card and the WISC mazes, both in favor of the LGG/RT+ group. In LGG/RT+ group, no differences found neither in mean test scores between pts with the radiation dose above and those with the dose below the median (56 Gy) nor in the interval from diagnosis
Taphoorn et al. 1992	A Total Cognitive Problem Score (TGPS) calculated by performances on 8 tests: d2- Test; **selective concentration**, Stroop- Color Word Task; **exclusive concentration**, Rey- Auditory Verbal Learning Test; **immediate & delayed recall**, Visual Association Test; **episodic memory**, Categoric word retrieval; **verbal fluency,** Judgment of Line Orientation; **spatial insight**, Facial recognition test; **gestalt recognition**, WISC Maze test; **foresight & planning**. The TGPS was divided into a 3 point scale from 0 (normal), 1 (lowered) to 2 (disturbed)	5 cases TGPS range was 0.69–1.21 (high cognitive impairment), 6 cases was 0–0.55 (low cognitive impairment)
Surma-aho et al. 2001	5 test variables: Digit Span Similarities subtests; **verbal IQ & verbal memory and free recall (similarities),** Block Design and Digit Symbol subtests (Wechsler Adult Intelligence Scale); **performance IQ,** Modified Benton Visual Retention Test (MBVRT first reproduction and percentage forgotten); **visual memory & attention**	Significantly worse tests results found in RT+ group than in RT−, especially in the MBVRT forgetting percentage. No significant differences found in any 5 test variables between whole/focal irradiation pts. The severity of leukoencephalopathy both in resected & non-resected hemispheres was significantly relates to poor memory performance in the RT+ group but not in the RT− group
Shih et al. 2015	Wechsler Adult Intelligence Scale (WAIS)- III Full scale IQ; **Intellectual Functioning,** WAIS-III Perceptual Organization Index; **Visuospatial ability,** WAIS-III Verbal Comprehension Index, Boston Naming Test, Auditory Naming Test; **Language,** WAIS-III Working Memory Index and Spatial Span; Continuous Performance Test: Inattention Score and Vigilance Score; **Attention & working memory,** WAIS-III Processing Speed Index; Trail Making Test A; **Processing speed,** Trail Making Test B; Controlled Oral Word Association Test F-A-S; Wisconsin Card Sorting Test; Continuous Performance Test Impulsivity Score; **Executive function,** Hopkins Verbal Learning Test-R (HVLT-R): Total Recall, Delayed Recall, and Retention; **Verbal memory,** Brief Visual Memory Test-R (BVMT-R): Total Recall and Delayed Recall; **Visual memory,** HVLT-R Total Recall; WMS-III Trails A and Trails B; Controlled Oral Word Association Test F-A-S; **Clinical trials battery**	8 pts exhibited baseline impairment before radiation in 1 or more of the language, visual or verbal memory, or processing speed domains. Performances in all neurocognitive domains remained stable or improved marginally over time for all pts
Sherman et al. 2016	WAIS-III Full Scale IQ; **Intellectual functioning,** WAIS-III Perceptual Organization; **Visuospatial ability,** WAIS-III Verbal Comprehension, Boston Naming Test, Auditory Naming Test; **Language,** WAIS-III Working Memory, WMS-III Spatial Span, Conners' continuous Performance Test (CPT-II) Inattention, CPT-II Vigilance; **Attention & working memory,** WAIS-III Processing Speed, Trail Making Test Part A; **Processing speed,** Trail Making Test part B, Controlled oral word association test (COWAT) F-A-S, Wisconsin card sorting test (WCST) Errors, CPT-II Impulsivity; **Executive function,** HVLT-R Total Recall, HVLT-R Delayed Recall, HVLT-R Retention; **Verbal memory,** BVMT-R Total Recall, BVMT-R Delayed Recall; **Visual memory,** HVLT-R Total Recall, Trail Making Test Part A, Trail Making Test Part B, COWAT F-A-S; **Clinical trials battery**	Pts at baseline were not significantly impaired compared to normative data in any assessed cognitive domain. At baseline, pts with left-sided tumors performed significantly worse than those with right-sided tumors on measures of verbal memory. Cognitive functioning of entire group remained largely stable over time, but the left-sided tumor pts had greater improvement in verbal memory performances & Clinical Trial Battery. No significant cognitive differences were found according to tumor size
Laack et al. 2005	Cognitive functions; **verbal and visual- spatial intelligence**, **immediate verbal & visual memory**, **long term verbal memory**, **cognitive flexibility**, **psychomotor skills**, **alertness & concentration**, **language** were tested by Folstein MMSE, WAIS-R (Revised), AVLT, Benton Visual Retention Test (BVRT), Trail-Making Test (TMT), Stroop Color-Word Test, COWAT. Furthermore, the performance in the aforementioned cognitive functions was graded clinically on a scale ranged from −4 to +1 [(−4 = severe impairment), (−3 = moderate impairment), (−2 = mild impairment), (−1 = borderline impairment), (0 = normal), (+1 = above average)], in which, any 2-point change in these ratings was considered clinically significant	No statistically significant declines in cognitive function after RT. More precisely, Baseline: Lower overall cognitive performance was found in both RT groups, with no statistical difference between them. Tumor/pts variables were not found to be associated with cognitive functioning. Second evaluation: Higher scores in all psychometric measures; only WAIS-R (index for non-verbal problem-solving ability) scores meet statistically significant increase. No statistically significant changes between to RT groups. Third & more evaluations (10/20 pts had): Stable cognitive performance of pts. No statistically significant difference of 2nd evaluation cognitive performance among pts underwent two evaluations vs those with 3. Pts that respond to RT had a median of 1 point improvement on their MMSE score than non-responders ($p = 0.02$). Clinically significant change in cognitive function according to the clinical scale created: 11/20 pts were stable. 5/20 pts had improvement in the domains of immediate verbal memory, learning, long-term verbal memory, cognitive flexibility & spatial problem solving. Complex reasoning skills of one

Table 2b (*continued*)

Author	Cognitive functions studied	Primary outcome (Cognitive function)
		pt (1/5) improved from −2 to 0 after 18mo, but declined back to baseline after 3ys. 4/20 had decline in one or more domains of immediate verbal memory, learning, spatial problem solving. All declined pts were from high RT dose group
Brown et al. 2003	Folstein MMSE over time; clinically significant change was considered a 3-point change on MMSE from baseline	Baseline: 36 pts had abnormal MMSE (0–26), 151 pts had normal MMSE (27–30) Year 1, 2, 5: Only 8%, 5% & 5% of pts assessed on year 1, 2 & 3 respectively, with available baseline MMSE had clinically significant decrease in score. 8%, 4% & 6% of pts assessed on year 1,2 &3 respectively, with normal baseline MMSE had clinically significant decrease in score whereas 92%, 96% & 94& were stable. 12%, 12% & 0% of pts assessed on year 1, 2&3 respectively, with abnormal baseline MMSE had clinically significant decrease in score, whereas 29%, 38% & 33% were stable and 59%, 50% & 67% had clinically significant increase. Among the three cognitive different groups (clinically significant increase in score, stable score, clinically significant decrease in score) no significant differences were found at any key evaluations in the distributions of age, sex, tumor size, tumor location, tumor histologic type, NFS, seizures, seizure medication, radiation dose, conventional versus conformal radiotherapy (conventional defined as two or fewer fields, conformal defined as three or more fields), and number of radiation fields
Douw et al. 09	Letter-digit substitution test, Concept-shifting test, Stroop test, visual verbal learning test, memory comparison test, categoric word fluency	Significantly worse on executive functioning, information processing speed and attention, between groups. Attention (significant decline in repeated measures)
Klein et al 2002	Intelligence (Dutch adult reading test) perception (line bisection, facial recognition, judgement of line orientation, LDST), memory (VVLT, WMT) attention & executive function (Stroop, categoric word fluency, concept shifting test) one year post diagnosis, no radiological recurrence before testing within 3 months	Both irradiated and non-irradiated patients exhibited worse cognitive results. Cognitive decline attributed to the tumor itself
Prabhu et al 2014	MMSE	No decline in MMSE score

diminished baseline MMSE scores actually experienced improvement following RT. This was most apparent in the study by Brown et al. [43], in which 59% of the patients with abnormal baseline MMSE scores improved more than 3 points in the 1st year, a percentage that was sustained in the next follow up assessments and was also apparent in the Prabhu et al. [47] study in patients with MMSE score <27. Yavas et al. [45] also noted that baseline MMSE scores exhibited a statistically significant deficit in recall, with follow up evaluation showing a trend towards improvement. This baseline deficit in the recall subcomponent was noted in Brown et al. [43] as well. In their follow up post-RT assessments, when a decline was observed it was mostly encountered in serial sevens (measure of executive function) and language.

A full scale IQ test (Wechler Adult Intelligence scale III) was employed by one research group in 20 patients receiving proton beam therapy, with results reported in two papers [39] Their performance in the follow up assessments of up to 5 years post proton radiation therapy (provided that the patients remained free of disease progression) did not differ significantly from their base line performance, rising on average 0.07 standard deviations per year within the 5 year observation period.

Nine studies assessed the effects of RT on specific cognitive domains, namely executive function, attention, memory, language and visuospatial skills.

Sherman et al and Shih et al evaluated executive function using the Wisconsin Card Sorting test (a measure of retained attention, working memory, abstract thinking and set shifting; [48], trail making test B (assessing visual search, scanning, speed of processing, mental flexibility, and executive functions; [49], and Concept shifting task (measuring sustained attention; [50]. They found that executive functions in fact improved in the follow up assessment of patients receiving proton beam therapy. Laack et al. [46] also employed the Trail making Test A & B [49] and did not find any difference in the post RT follow-ups compared with baseline scores. Douw et al used the Concept shifting test as a measure of executive and psychomotor function along with categoric world fluency, both of which were deemed deficient.

WISC maze test measures planning and foresight [51]. Surprisingly, the Taphoorn [41] LGG/RT+ group performed significantly better in the WISC maze test compared to the LGG group that did not receive RT. Surma-aho and colleagues [42] used the Performance IQ subcomponent, which consists of Block test (spatial ability[52] and letter digit substitution, and encountered significantly worse performance for the radiotherapy group. Stroop test measures selective attention, cognitive flexibility and processing speed [53]. Laack did not find any effect of RT on Stoop test performance. Interestingly, Douw et al report worse performance for RT patients compared to non RT patients, while Taphoorn et al describe statistically significant faster times for the RT group. Letter digit substitution test evaluates psychomotor speed [54]. In an interesting retrospective study looking at cognitive function at 12 years follow up, Douw et al., [37] showed that RT resulted in decline in executive function, information processing, speed and attention, while Klein's [38] patients did not perform overall worse. However, patients receiving fraction doses >2 Gy did exhibit memory impairment (see section below; [38]).

Memory and recall functions were assessed by the Benton visual retention test (specifically visual memory and perception; [55]. It was used by Laack et al. [46] who didn't detect any significant decline from the baseline performance at 3 years follow up and by Shih & Sherman who also did not find significant change in performance compared to the normative group (follow-up up to 5 years; [39,40]). On the contrary, Surma-aho et al. [42], with a mean follow up period of 7 years found significant decline in the percentage of items forgotten in the second reproduction of the test. Taphoorn and colleagues [56] do not note impairment on the visual association test, a battery for visual recall [57]. Klein [38] used a working memory task and revealed a significant and dose-dependent decline in working memory capacity in those patients who received fraction doses >2 Gy.

Auditory verbal learning task appraises numerous aspects of memory acquisition and retrieval such as storage, consolidation over short or long time intervals and access via free retrieval or recognition [58]. In the Taphoorn et al. [56] study, with a mean of 1 year follow up, the radiotherapy group was deficient. In the Taphoorn et al. [41] study, with a mean follow up of 3.5 years, immediate recall was most affected with delayed recall exhibiting impairment too, though this difference can be attributed to the imbalanced sample of LGG/RT+ patient group, which was heavily biased towards left hemisphere gliomas. In contrast, Laack et al [46], with a mean follow up of 3 years, did not show any deficits in RT patients compared to their baseline performance. Sherman [40] & Shih [39] employed the Hopkins verbal learning test to evaluate verbal memory [59] and report improvement from their base line performance following proton RT (follow up on both reports was 60 months).

The visuo-verbal learning task (VVLT) assesses both memory and language [48]. In this test, the Douw et al. [37] RT+ group performed on their post RT follow up evaluation (12 years) on par with their base line performance and on par with the performance of the control group. Klein, on the other hand reported significantly deficient performance of radiotherapy patients on the VVLT at 6 years follow up. Shih et al. [39] used the Boston naming index and COWAT to evaluate language functions [48] and found no discernible difference in performance. COWAT, however, was also used by Douw et al. [37] who used it as a measure of executive functioning which was impaired in RT group at 12 years follow up. On the other hand, Klein [38] and Taphoorn [56] did not detect any significant difference in performance between groups in this test in a 3.5–6 years follow up.

Visuospatial faculties and other functions were evaluated by Klein et al. [38] using line bisection, line substitution, facial recognition and line orientation. The authors report diminished performance merely in 1 out of 7 tests. Line substitution and facial recognition was also employed by Taphoorn et al. [56], without a documented deficit.

Discussion

The aim of this systematic review is to evaluate the effects of brain radiotherapy on cognition in grade II adult glioma patients. Overall, an effect in general intelligence was not encountered in the single group that tracked it. Executive function was documented as deficient in two out of 5 cognitive batteries [37,42]. Douw and colleagues [37] were the only group out of 4 that reported attentional decline in two separate tests. Memory defects were seen in three studies [38,41,42], whereas in three different studies no effect was reported. Language impairment was documented in one out of two language batteries in the Klein et al study [38], while four other studies did not detect any negative cognitive impact. Interestingly none of the prospective studies did document any decline in any cognitive domain tested [43,45–47,39,40]. An overview of these findings are provided in Table 3.

Past literature reviews handling broader questions about the cognitive effects of neuro-oncological treatment options did encounter the issue of the potential cognitive radiotoxicity in grade II glioma patients and noted the impasse of inconclusive and conflicting results. Shields and Choucair [60] acknowledge the concerns on the impact of RT on neurocognitive function and HRQoL while Saad and Wang [61] iterate the past findings on the detrimental RT effects on cognition along with doubts about confounding effects. McAleer and Brown [62] also emphasize inconclusive findings, confounders and employment of previous high dosage or high fraction radiation techniques. Lawrie et al. [63], in a recent meticulous Cochrane review, conducted a meta-analysis on the adjoined data of the Klein et al. [38]/Douw [37] cohort and the Vigliani et al. [64] cohort and could not document a significant association of RT with long term neurocognitive impairment and judge the quality of evidence as "very low". Vigliani and colleagues failed to show a substantial cognitive decline using a detailed battery in a 4 year follow up. The most current data on the cognitive effects of radiotherapy stem from the EORTC 20033-26033 trial; within the one year follow up period no significant deficit in memory functioning (tested using the Visual Verbal Learning Test) was documented in the 53 patients receiving radiation therapy compared to 46 patients receiving temozolomide chemotherapy [65]. The Vigliani et al. [64] and the Klein et al. [65] studies were not incorporated in our analysis as their cohorts admitted patients receiving chemotherapy and hence did not meet our inclusion criteria.

These inconsistent results are reflective of the challenges encountered in assessing the cognitive effects of RT in grade II glioma patients. As doses and fraction sizes became more modest, the radiation effects can be less evident. The majority of the studies included small samples, with four studies enrolling less than 30 LGG patients per study [39–42,56]. As a result, there might be low statistical power to detect effects that may actually exist. This point is most relevant in the proton beam studies by Sherman and Shih, who did not document any cognitive effect. Opting for proton beam therapy versus photon radiation therapy is motivated by the fact that the characteristic depth-dose distribution of protons achieves higher conformality and therefore results in potentially less irradiation of healthy tissue [66]. On the other hand the distal end of the Bragg peak might lie close to eloquent structures (e.g. hippocampus) and conceivably result in higher morbidity [67]. At any rate, the sample size of the Sherman and Shih studies (n = 20) does not provide enough statistical power to safely argue for equivalence of proton beam LGG patients with the normative group.

A full neurocognitive assessment is a time-consuming and arduous endeavor. Thus, Brown et al. [43] were able to gather a sizable sample of 203 patients that were evaluated through the MMSE. Although MMSE is fast and practical, it lacks in sensitivity and more importantly was not designed for detailed evaluation of cognitive performance. General intelligence tests (e.g. employed by Sherman [40] and Shih [39] can be very detailed measures of general intellectual functions but may be inappropriate tools to assess the potential deficits in specific domains experienced by grade II glioma patients. The ease of administration drove 4 groups to employ them in their prospective trials providing a total sample of 376 patients. Only two studies [37,38] offered sizable samples and full neurocognitive evaluations, however both of them were retrospective. A summary of the above can be found in Table 2.

A crucial reason, we suspect, for the inconsistent results reported is the fact that the cognitive effects may develop slowly over a long period of time [68,69]. This puts forward the requirement for appropriate and consistent timing of the follow up assessments. For instance, Klein et al, while they offer the largest LGG sample with full cognitive evaluation, their assessments were performed anywhere between 1 year and 22 years post radiation therapy. Prospective studies such as these of Laack [46], Sherman [40] and Shih [39], kept a consistent assessment schedule that extended up to 3–5 years. The stipulation for protracted follow-up brings forth two potential issues that may diminish the effects measured. The first one is attrition bias, namely, the worst performing patients are the most likely to be lost in the follow up assessments and the second is practice effects [46] i.e. as patients are repeatedly evaluated on the same tests they become increasingly familiarized with the content and the procedure (Table 3).

Addressing confounders is an additional and vital hurdle. Age, performance status, repeat operations, extent of resection and subclinical tumor progression can affect cognitive performance [43].

Table 3
Studies' results on radiotherapy-associated impairment at various components of cognition in grade II glioma patients. In bold with asterisks studies with statistically significant findings. Studies with prospective design are underlined.

Cognitive Domain	Tests	Impaired out of total tested	Studies (Studies with statistically significant findings are marked in bold with asterisk)
General intelligence	MMSE	0/4	[43,45,46,47]
	Full scale IQ test	0/1	[39,40]
	SUM	***0/5***	
Executive function	Trail making test	0/2	[39,40,46]
	Concept Shifting Test (CST)	1/2	[39,40], *[37]
	Wisconsin Card Sorting Test (WCST)	0/2	[39,40,41]
	Controlled Oral Word Association Test (COWAT), Categoric fluency	1/4	* [37,39,38,56]
	SUM	***2/10***	
Attention	Stoop	1/3	* [37,56,46]
	Letter Digit Substitution Test (LDST)	1/2	* [37,38]
	SUM	***2/5***	
Memory	Benton Visual Retention Test (BVRT)	1/3	* [42,39,40,46]
	Visual association test (VAT)	0/1	[56]
	Working Memory test	1/1	* [38]
	Rey Auditory Verbal Learning Test (AVLT)	1/2	* [56,46]
	Hopkins Verbal Learning Test (HVLT)	0/1	[39,40]
	SUM	***3/8***	
Language	Visuo Verbal Learning Task (VVLT	1/2	* [38,37]
	COWAT, Categoric fluency	1/4	* [37,39,40,38,56]
	SUM	***2/6***	
Visuospatial	Various tests	1/9	* [38,56]

Anti-seizure medication can produce remarkable impairment on psychomotor speed in perceptual tasks [38]. However, the most important and difficult confounder to overcome is tumor location, particularly in cases where eloquent cerebral areas are involved [38]. Notably, if no care is taken to address this confounder, standard medical practice will lead to a distinct selection bias, as patients with tumors in eloquent areas are less likely to receive gross total resection and thus more likely to be assigned to the radiotherapy group. This is evident in the Taphoorn et al. [41] study, in which the RT group mainly consisted of left hemisphere LGG patients. This selection bias is less obvious but present in both Klein and Douw studies, in which radiotherapy groups were more likely to receive biopsy instead of resection. Imperfect group composition was also seen in the Surma-aho study [42], in which a significant portion of patients (17 out of 26 in the RT+ group) were subjected to whole brain radiation. Accordingly, in the Klein and colleagues study [38], 10% of the patients received whole brain radiation while a significant number was treated with fractions over 2 Gy (17.3% of the patients). It should be stressed that the Klein [38]/Douw [37] cohort which showcased the starkest effects in multiple cognitive domains received the most protracted follow up, namely 12 years. This raises the strong possibility that cognitive decline following radiotherapy may be manifested after many years and therefore the importance of long term follow up for these patients is vital. This might be the reason that studies with short observation periods, such as this of Vigliani et al. [64] may fail to uncover any cognitive deficit.

Prospective trials by design assure a known baseline cognitive score, consistent follow up and a tighter control of the confounding variables. Five studies meeting our inclusion criteria had a prospective design, however the three larger ones which provided more than half of the population sample of our data (376 patients), employed exclusively the Mini Mental State Exam, a quick dementia screening which can be considered inadequate for the use as neurocognitive assessment tool. The two prospective trials providing full neurocognitive assessments are those of Shih et al./Sherman et al. [39,40] and Laack et al. [46] which collectively provide a sample of just 40 patients. Given this, confident evidence about the cognitive effects of RT on this cohort ought to be drawn by a due prospective trial with full neurocognitive assessment, large sample size and meticulous confounder control.

The awareness of the cognitive effects of hippocampal irradiation led to the development of radiation therapy administration strategies which minimized cognitive injury [26]. The advent of intensity modulated radiotherapy enabled accurate treatment plans with appropriate hippocampal avoidance in either whole brain radiotherapy plans for brain metastases (with optional combined stereotactic radiotherapy boosting) [70] or partial brain radiotherapy for primary brain neoplasms [71]. Volumetric modulated arc therapy further facilitated the ability to obtain acceptable and homogeneous target volume coverage [72].

Establishing the cognitive effects of therapy on grade II glioma patients is part of a broader effort to answer how the health-related quality of life (HRQoL) is influenced and which factors have the most detrimental effect. Health related quality of life is a patient assessed evaluation consisting of the physical, psychological, emotional an social changes in their daily life [73]. The tumor itself is at least partly responsible for a decline in HRQoL; tumor related neurological deficits and seizures affect every day functions [18], while neuro-oncological patients often exhibit depression–like symptoms [74]. Therapeutic interventions can have a complex interplay with the parameters controlling HRQoL outcomes. For instance, surgical resection is potentially associated with new post- operative morbidity that reduces HRQoL. Conversely, surgery can improve HRQoL by diminishing the tumor associated morbidity [5]. Accordingly, antiepileptic medication side effects can decrease HRQoL, but poor seizure control is associated with low HRQoL scores as well [75]. In the same vein, radiation therapy can delay tumor progression but may negatively affect HRQoL [76]. Moreover these effects on HRQoL may develop late; a secondary analysis or the EORTC 22033–26033 did not document independent association of radiation therapy with decline in HRQoL within 2 years [77], while Boele et al. [78] report long term decline several years post diagnosis despite stable disease.

These thoughts are particularly relevant especially in the context of the ongoing 1608-EORTC-BTG phase III study (I-WOT) which aims to investigate whether early treatment of surgically treated IDH mutated 1p/19q intact astrocytoma patients combined with chemotherapy would improve outcome and would outweigh potential complications including those of neurocognition and quality of life. Whilst the I-WOT study is to be commended for the planned detailed neuro-cognitive assessments, there remains understandable concern from many surgeons of recruiting patients to a study which gives up-front radiotherapy even in young patients with a complete resection [74].

Past literature reviews have provided a cursory handling of the issue of radiotherapy's cognitive effects in grade II glioma patients as they had broader scopes, either addressing neurocognitive outcomes of all therapeutic interventions in grade II glioma patients or tackling the impact of RT in the context of all brain tumors, including high gliomas [60–63]. This review provides the first focused and systematic assembly of available evidence on radiotherapy's cognitive effects in grade II glioma patients with an explicit aim to sidestep the known major confounders of chemotherapy and of mixed oncological cohorts. This comprehensive overview illuminates the unaddressed shortcomings of these studies and yields a straightforward roadmap for future studies. While conclusive evidence are yet to arrive, this review facilitates moving forward from the notion that modern radiotherapy protocols do cause cognitive deficits of indeterminate profile and magnitude in grade II glioma patients [63] to the recognition that current data cannot affirm that RT is associated with substantial cognitive decline in this cohort.

Conclusion

While considerable and serious effort has been made to address the cognitive effects of low fraction focal radiotherapy in grade II glioma patients, indeed conflicting results remain and the main confounding factor—the local tumor effect—remains incompletely addressed. Concerns about the impact of radiation therapy on the cognitive function of grade II glioma patients are legitimate, however, current data fail to produce a consistent, coherent and ultimately convincing picture of the RT associated cognitive deficits. Notably, the most recent neurocognitive study in this cohort by Klein et al. [65] produced results in line with this conclusion. Upcoming studies may very well provide higher quality data to the contrary, but at present it is tenuous to argue that radiation associated cognitive morbidity outweighs the benefit of prolonged survival.

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Conflict of Interest

The authors report no conflict of interest regarding the materials or methods used in this study or the findings specified in this paper.

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Consent to participate

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