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RADIATION-INDUCED COGNITIVE IMPAIRMENT IN OLDER ADULTS – A REVIEW

Abstract

Radiation-induced cognitive impairment (RICI) is a recognized potential complication of radiotherapy in patients with primary and secondary brain tumors. Cognitive impairment is particularly relevant to older adults; however, most trials exclude them, resulting in paucity of information regarding the effects of radiotherapy in this population. As the population ages, the incidence of patients with primary brain tumors and brain metastases will also increase. Given the trend, further information is needed to recognize the effects of radiotherapy on cognitive function in the older adult population. Increased awareness regarding RICI is required due to the implications it carries for patient, caregivers, and treating physicians. This review highlights the mechanism of radiation-induced brain injury focusing on RICI and radiotherapy techniques developed to minimize the occurrence of RICI.

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INTRODUCTION

Around 70% of all cancers occur in older patients.[1] Glioblastoma multiforme (GBM) is the most common primary brain tumor, of which more than 50% are diagnosed in patients aged 65 and above.[2] As the population ages, the incidence of brain cancers is expected to increase.[2] Older adults are under-represented in studies for multiple reasons, including strict inclusion criteria which exclude patients with poor performance status and/or multiple comorbidities, concerns regarding treatment toxicities, and patient or family preferences.[2,3] For these reasons, cancer treatments given to older adults are based on trials conducted on non-representative samples of younger patients or fit older adults.[4] Furthermore, the advances in treatments focus mostly on prolonging survival which may not be the primary goal for some older adults.[5]

Cognition is important to many older patients, and consequently, identifying potential effects of treatment on cognition is important when deciding on cancer therapy.[2] Neurotoxicity, from radiotherapy alone or combined treatment of radiotherapy with chemotherapy, is more frequently seen in older adults.[6] This has implications for patients, caregivers, and clinicians. Patients need to be aware of possible side effects of treatments as that may affect their willingness to undergo treatment.[3] Since most cancer therapies are administered in an outpatient setting, caregivers should be aware of the increased support older adults may need, as radiation may further deteriorate baseline cognition.[3] Finally, for physicians, the risk of cognitive decline versus benefit of prolonged survival with treatment may influence which treatments are offered to patients, including what alternative options are considered.[2,7] We review radiation-induced cognitive impairment (RICI), its manifestations, natural history, and methods to mitigate its occurrence.

METHODS

We searched PubMed and Ovid Medline for articles published in English between 1946 and May 2021 with the assistance of a medical librarian. Terms used included "radiotherapy" and "radiation therapy", "brain cancer" and "brain neoplasms", "elderly", "aged", "geriatric", and "cognitive dysfunction". Our inclusion criteria was radiotherapy for primary and secondary malignant brain tumors and older patients defined as those aged 65 or older. We supplemented this with a search on Google for articles on cognition in cancer. We excluded benign tumors.

RADIATION-INDUCED BRAIN INJURY AND RADIATION-INDUCED COGNITIVE IMPAIRMENT

Radiation-induced brain injury (RIBI) is a syndrome of functional and anatomical deficits post-radiotherapy. It is a well-established side effect of radiotherapy in cancer patients, especially in older adults.[8] The three phases of RIBI are acute, early delayed, and late delayed (Table 1).

Table 1. Radiation-Induced Brain Injury Stages and Characteristics.

Radiation-Induced Brain Injury Stage	Reversibility	Timeline	Symptoms	Pathology
Acute	Generally transient	Within days after treatment	Headache, drowsiness	Edema, disruption of Blood-Brain Barrier

Radiation-Induced Brain Injury Stage	Reversibility	Timeline	Symptoms	Pathology
Early Delayed	Generally reversible	Weeks to 6 months after treatment	Somnolence, attention deficit, short-term memory loss	Transient demyelination
Late Delayed	Irreversible, progressive	6 months to years after treatment (Recommendation is to perform prospective and longitudinal follow-up studies to assess cognition prior to the start of treatment and over time, rather than after treatment alone, to identify whether cognitive impairment is present at baseline and specific domains affected by the cancer itself or treatment interventions)	Irreversible radiation-induced cognitive impairment (RICI)	White matter necrosis, permanent demyelination, gliosis, vascular abnormalities, hippocampal injury

Radiation-induced cognitive impairment (RICI) is the most commonly recognized side effect of radiotherapy in patients with primary and secondary brain cancers.[6,9] Irreversible RICI is seen in the late, delayed phase of RIBI.

The main cognitive domains affected by radiotherapy are memory, executive function, attention, and visuomotor speed which are thought to be attributed to radiotherapy induced frontal and subcortical dysfunction.[9] Neuropsychological assessment guidelines in brain tumor clinical trials have been published based on these findings. The recommendations are to perform prospective studies and longitudinal follow-up studies to assess cognition prior to the start of treatment and over time, rather than testing post treatment alone, as it is important to know whether cognitive impairment is present at baseline and the specific domains affected by the cancer itself or by treatment interventions.[10]

Multiple methods are used to assess RICI in clinical trials (Table 2). The Mini-Mental State Exam (MMSE) is the most frequently used screening tool for cognitive impairment in brain metastasis, likely because it is short and easy to use, however, it is insensitive and does not detect early cognitive changes, nor does it test executive function.[9,11,12,13] When comparing brain cancer patients using both the MMSE and the Montreal Cognitive Assessment (MoCA), 50% of patients with normal MMSE scores had abnormal MoCA scores.[11,14] Additional tools used in trials include the Trail-Making Test A and B (TMT-A and TMT-B) for visuo-motor speed and executive function, and the Hopkins Verbal Learning Test (HVLT), which is the most frequently used tool for memory and verbal learning in brain tumor trials.[9,11,15,16]. The International Cancer and Cognition Task Force (ICCTF) recommends the HVLT–Revised, the Controlled Oral Word Association Test (COWA), and the TMT as cognitive tests to follow up treatment effects on learning and memory, processing speed, and executive function for all cancer- related cognitive impairment, as those are the domains that have been shown to be mostly affected by radiation therapy.[17,18]

Table 2. Neurocognitive Tests used in Clinical Trials for Brain Tumors.

Tool	Domains tested	Description of the Tool
Mini-Mental State Exam (MMSE)	Global Neurocognitive Function: Orientation Registration Attention/calculation Memory Language and Verbal fluency Visual Construction	-Orientation: year, season, month, date, time, country, town, district, hospital, ward/floor -Registration: word repetition -Attention and calculation: serial subtraction, spell WORLD backwards -Delayed Recall -Language: naming objects, sentence repetition, follow 3 stage command, follow written instruction, write a sentence -Copying an image
Montreal Cognitive Assessment (MoCA)	Memory Executive function Visuo-spatial function Attention Abstraction Language Orientation	-Visuo-spatial: drawing/copying an image, alternate trail making, clock drawing -Naming: name the animal in the picture -Attention: forward and backward digit span, serial subtraction, vigilance -Language: sentence repetition, verbal fluency -Abstraction: explain how each pair of words are similar -Memory: delayed recall (5 words) -Orientation: date, month, year, day, place, city
Hopkins Verbal Learning Test (HVLT) and HVLT-Revised (HVLT-R)	Verbal Learning Memory	-HVLT tests short term recall, and recognition of words (HVLT-R also includes testing delayed recall)
Auditory Verbal Learning Test (AVLT)	Verbal Memory	-15 word lists are read out for the patient to learn and recall: done 5 times
Controlled Oral Word Association (COWA) Test[17]	Verbal Fluency Executive Function	-List as many words beginning with a certain letter of the alphabet in one minute: 3 different letters, total of 3 minutes
Paced Auditory Serial Addition Test (PASAT)[20]	Sustained Attention Auditory information processing	-Every 3 seconds a single digit is given to add to the previous digit

Tool	Domains tested	Description of the Tool
Trails Making Test A	Visuo-motor speed	-Connect numbers 1-25 in ascending order
Trails Making Test B	Executive function Visuo-motor speed	-Connect number to letter in ascending order

The extent to which radiotherapy causes cognitive impairment is difficult to determine. Confounding factors, including concomitant treatment with chemotherapy, commonly used medications like anti-epileptics and corticosteroids, and the size and location of the brain tumor also play a role in cognitive changes.[7,10] Some studies looked at effects on cognition in cancer patients without brain tumors, such as those receiving prophylactic cranial irradiation (PCI).[9] A randomized trial of 314 patients with small cell lung cancer allocated patients to PCI versus non-PCI and found that 31% of the PCI group had impaired processing speed, sustained attention, and verbal memory compared to 17% in the non-PCI group (impairment defined as a patient scoring less than 21 correct answers on the addition of consecutive numbers on the Paced Auditory Serial Addition Task (PASAT), low memory score on the Rey-Osterrieth Complex Figure Test (ROCF), and recall of less than 5 out of 15 items on the learning component of the Auditory Verbal Learning Test (AVLT) or recall of less than 4 items in the retention component of the AVLT).[19,20,21]). Although the population is not comparable to the patients with diagnosed brain tumors, the study does provide insight to the most affected cognitive domains.

RADIOTHERAPY TECHNIQUES AND RICI AVOIDANCE

Whole-brain radiation therapy (WBRT) remains a crucial strategy in the treatment of brain tumors as it targets the entire brain, including microscopic lesions. RICI is a particularly feared side effect of radiotherapy in managing older patients with brain tumors.[6] Because of the potential for neurotoxicity - especially in the frontal and subcortical areas of the brain impacting executive function, visuo-motor speed, and attention, and in the hippocampus, which is the center for memory and learning - alternative techniques to WBRT are being offered (Table 3).[10,22,23]

Table 3: Brain-Related Radiotherapy Techniques and Their Definitions.

Radiotherapy technique	Definition
Whole Brain Radiation Therapy (WBRT)	Radiotherapy that targets the entire brain, treating even microscopic non-visible lesions. Usually consists of 5-15 sessions of radiotherapy.
Stereotactic Radiosurgery (SRS)	Personalized, highly precise radiotherapy delivered directly to visible cranial and extracranial targets. SRS utilizes a high dose of radiotherapy in a single to few sessions.
Gamma Knife Surgery	One of the machines used to deliver SRS, using Gamma-ray from a Cobalt radioactive source.
Cyber-Knife	One of the machines used to deliver SRS, using X-ray from a linear accelerator.
Intensity Modulated Radiotherapy (IMRT) and Simultaneous Integrated Boost (SIB)	Differential radiation doses per session delivered to selected regions during the same treatment session, leading to different total doses given to targets in the same number of sessions

In particular, techniques that include hippocampal avoidance (HA) may result in less impairment post-radiotherapy and may preserve quality of life.[24,25] Though these techniques have been shown to reduce cognitive side effects, increased surveillance for recurrence of disease and possible increased requirements for salvage treatment may be needed.

Intensity Modulated Radiotherapy and Simultaneous Integrated Boost

A single arm phase II study by Gondi *et al.* suggested that treating patients with brain metastases with WBRT with HA, using Intensity Modulated Radiotherapy (IMRT) can help preserve cognition, especially memory. As assessed by the HVLT-R, 7% of patients receiving WBRT with HA developed RICI, compared to a historical control of 30% in patients treated with WBRT without HA.[25] Patients aged 60 years and older were at higher risk for RICI. Another study evaluating 32 patients with a median age of 63.5 years (age range 45.3-78.8 years) found that WBRT with HA can help preserve cognition compared to WBRT without HA, as assessed by the physician according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).[26,27]

Stereotactic Radiosurgery

Another technique to spare normal brain tissue from exposure to radiotherapy is stereotactic radiosurgery (SRS). SRS allows for delivery of high-dose radiation directly to the tumor without affecting other areas of the brain. Trials comparing SRS to WBRT with respect to neurotoxicity and cognitive impairment have been done. A study by Aoyama *et al.* of 132 patients with brain metastases which randomized patients to SRS+WBRT (median age 62.5 years) versus SRS alone (median age 62.1 years) found no difference in neurocognitive function as assessed by MMSE.[28] This may be because MMSE is not sensitive in detecting mild cognitive impairment, especially executive dysfunction, or due to the small sample size, limiting power to detect small differences. On the other hand, another study of patients with brain metastases, comparing SRS with WBRT versus SRS alone, showed a significant decline in cognitive function involving learning and memory, with a 52% decline in the HTLV-R total recall in the SRS with WBRT group versus 24% in SRS alone group at 4 months. It concluded that SRS alone is preferred for preservation of learning and memory with regular clinical monitoring due to increased risk of disease recurrence in the SRS alone group. [29]

A multicenter phase 3 study comparing patients who received SRS alone versus WBRT post surgical resection of brain metastases found longer cognitive-deterioration-free survival in the SRS group (3.7 months; 95% CI 3.45-5.06) compared to the WBRT group (3.0 months; 95% CI 2.86-3.25), with no difference in survival.[30] Cognitive-deterioration-free survival was defined as the time from randomization to a greater than 1 standard deviation drop from baseline in any of the cognitive tests (HTLV-R, COWAT, TMT-A, and TMT-B). Based on these results, other studies are also implementing SRS as an alternative to WBRT.[31]

Avoidance of Radiotherapy

In certain tumors, avoidance of radiotherapy may be possible. Primary CNS lymphoma (PCNSL) is sensitive to both chemotherapy and radiotherapy.[6] In studies conducted between 2000-2018 on patients with median age ranging from 65 to 82 years, WBRT resulted in 19-83% of patients experiencing neurotoxicity, including cognitive impairment which was defined as the percentage of grade 3 and 4 toxicity as per the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). [6,27] Therefore, the trend has shifted to treat PCNSL with chemotherapy alone without radiotherapy. However, a lack of trials looking at chemotherapy-only treatments while omitting WBRT in older adults limits our knowledge of optimal management.[6]

EXPLORING POSSIBLE PHARMACOLOGICAL RICI MITIGATING STRATEGIES

Trials have been done to determine if pharmacological agents used for dementia, such as memantine and donepezil, have a neuroprotective effect in patients receiving radiotherapy. Strategies utilized pharmacological agents along with radiotherapy, preventatively, or post-radiotherapy, in those who have developed RICI have been studied.

In one trial, patients with brain metastases receiving WBRT were randomized to receive memantine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, or placebo within 3 days of initiation of radiation as a RICI prevention strategy.[32] Patients with MMSE score <19 were excluded. A battery of cognitive tests including HVLT, COWA, and MMSE were done at baseline, 8 weeks, 16 weeks, and 24 weeks, with the primary outcome being HVLT-Delayed Recall at 24 weeks. The study demonstrated a trend towards less decline in delayed recall (median decline 0 vs. -0.9 on the HVLT-delayed recall, p=0.059 after 24 weeks) in patients who received memantine vs. placebo. This did not meet statistical significance possibly due to a of lack of evaluable events due to greater than expected deaths and drop-out. The study did demonstrate, however, an improvement in time to cognitive failure (on any of the tests) with memantine (HR 0.78, p=0.01) with 53.8% of those on memantine vs. 64.9% on placebo experiencing a cognitive decline at 24 weeks. The results were promising as the cognitive decline was delayed in the memantine group.

Another study randomized patients who had completed radiotherapy to the brain (whole brain or partial brain irradiation) for at least 6 months and had no progression of disease for 3 months prior to enrollment to donepezil, an acetyl-cholinesterase inhibitor, at a dose of 5 mg daily for 6 weeks, then 10 mg daily for 18 weeks or placebo.[33] The study included patients regardless of their pre-treatment cognitive impairment, however, those who were already on medications to enhance cognition were excluded. Two-thirds of patients had radiotherapy for primary brain tumors, 27% for brain metastases, and 8% had prophylactic cranial irradiation. A battery of cognitive tests were assessed including HVLT-R, the modified Rey-Osterreith Complex Figure (ROCF), Trail Making Tests A and B (TMT-A and TMT-B), Controlled Oral Word Association Test (COWA), Digit Span Test (DST), and the Grooved Pegboard. The main outcome was the effect of donepezil on an overall composite score of these tests at 24 weeks. While no difference in the overall cognitive composite score was noted at 24 weeks with donepezil vs. placebo (least squares mean 0.22 vs. 0.19, p=0.48), cognition improved over the 24 weeks in both groups. However, improvements in preserving memory (HVLT-R recognition least squares mean 10.91 vs. 10.34, p=0.027; discrimination least squares mean 10.1 vs. 9.16, p=0.007), and motor speed and dexterity (Grooved Pegboard-Dominant hand least square means 105.1 vs. 116.99, p=0.016) were seen with donepezil vs. placebo. Significant interaction was noted between baseline pre-treatment cognition and outcomes of cognition with donepezil, suggesting that those with worse cognition prior to initiation of donepezil benefited the most. Although results appear promising, further trials are needed to assess whether medications have neuroprotective effects in brain tumor patients post-radiotherapy.

TAILORING CARE TO FITNESS WITH COMPREHENSIVE GERIATRIC ASSESSMENT

Although it is important to recognize and aim to prevent RICI in older adults, there is a subgroup of fit older adults who may benefit from standard radiotherapy treatment.[6] The French Association of Neuro-Oncology trial was conducted on patients aged 70 years and older with newly diagnosed glioblastoma multiforme or anaplastic astrocytoma and good performance status to assess the effect of radiotherapy compared to best supportive care.[34] The trial was terminated due to the superiority of radiotherapy over supportive care with respect to survival (median 29.1 weeks in the radiotherapy plus supportive care group, [95% CI, 25.4 to 34.9] versus 16.9 weeks in the supportive care only group, [95% CI, 13.4 to 21.4]) with no significant reduction in cognitive function in the radiotherapy group compared to best supportive care as measured by the MMSE and the Mattis Dementia Rating Scale (which tests multiple domains like attention, memory, and executive function). Although MMSE scores declined significantly in both groups, it was not worse in the radiotherapy group. Thus, in older adults, patients with good performance status should be considered for standard treatment despite its possible cognitive side effects.

A comprehensive geriatric assessment (CGA) may also help to decide optimal individualized cancer treatment options in older adults. A CGA involves a multidisciplinary assessment which evaluates modifiable and non-modifiable risk factors of frailty and identifies factors which can be managed to improve outcomes. Domains of a geriatric assessment include nutrition, function and mobility, polypharmacy, cognition, mood, and social circumstances.[5] The CGA can be used to allocate patients into three categories: the "fit", where patients are in good health and independent in activities of daily living (ADL); the "vulnerable", where comorbidities may exist, and patients need help with some ADLs; and the "frail", where patients have severe comorbidities and/or dependency for most ADLs.[3] These categories can be correlated with the Clinical Frailty Scale (CFS) with "fit" being CFS 1-3, "vulnerable" with CFS 4-6, and "frail" with CFS 7-9. [35] CGA facilitates individualized management approaches weighing risk versus benefit of treatments in older adults, and identifies those likely to benefit from standard treatment. The CGA also aims to prevent overtreatment of frail patients with poor performance status while preventing the under treatment of those who can tolerate treatment and may derive benefit from treatment. Fit patients should be offered the same treatment as younger patients, frail patients should receive best supportive care. Vulnerable patients should have modifiable factors addressed to try and optimize their health and may have modifications in their treatment. For more information, readers can review the Canadian Geriatric Oncology Meeting Report.[36]

The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Older Adult Oncology recommends a pre-treatment geriatric assessment for all older adults diagnosed with cancer being considered for anti-cancer therapy to identify those at increased risk of developing treatment toxicities.[5] A baseline quick cognitive screening tool like the Mini-Cog, which consists of a clock drawing test and 3-word recall, should be performed at minimum as part of the assessment and, if dementia is suspected, should undergo further comprehensive evaluation.

LIMITATIONS

Although our aim was to target adults aged 65 and above, most trials had a heterogenous age population of both younger and older adults. There was no uniform cognitive tool used for all the trials to assess cognition. While the MMSE was a commonly used tool, it is not sensitive in detecting mild cognitive impairment or executive dysfunction. Studies also used different primary outcomes and varying definitions of RICI with cognitive decline measured at different points in time. Inclusion of patients with different tumor types, sizes, locations, and radiation doses also make it difficult to attribute toxicities to radiation alone. Furthermore, trials tended to include younger and fitter patients, so little data is available on adults aged 65 and older, those with frailty, or with baseline mild cognitive impairment or dementia.

CONCLUSION

The incidence of brain tumors is expected to increase with the growth in the older adult population. Although prognosis remains relatively poor in brain cancers, advances in treatment and radiotherapy techniques can improve survival. It is imperative to understand the impact and anticipated effects of radiotherapy on cognition to help patients and caregivers make an informed decision regarding radiotherapy. CGA may help define who may benefit from treatment as the neurotoxic effects may be tolerated by fit older adults and unacceptable to those with poorer baseline performance status. As the geriatric oncology field grows, more trials should utilize quality of life and cognition as a primary outcome in the older adult population to help define the optimal treatment for this population while minimizing potential neurotoxic effects.

KEY POINTS
Radiotherapy is a common treatment in CNS tumors and is known to cause radiation-induced brain injury (RIBI), of which the late irreversible stage is radiation-induced cognitive impairment (RICI).
Older adults may be more vulnerable to developing RICI and the implications can be more significant.
The main cognitive domains affected by radiotherapy are memory, executive function, attention, and visuo-motor speed.
Whole-brain radiation therapy (WBRT) targets the whole brain, including microscopic lesions, but has the highest risk of RICI. Hippocampal avoidance strategies have been developed to reduce RICI, though regular surveillance for disease recurrence is needed.
Trials on memantine with initiation of radiotherapy as a RICI preventative measure, and donepezil post-radiotherapy, have shown promising results with less decline in certain cognitive domains compared to placebo.
Understanding RICI can help answer questions the patient and family might have pre- and post-treatment, thereby permitting more fully informed decisions.

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