The neurocognitive effects of radiation in adult low-grade glioma patients

Paul D. Brown, Jan C. Buckner, Joon H. Uhm, and Edward G. Shaw

Division of Radiation Oncology (P.D.B.), Division of Medical Oncology (J.C.B.), and Division of Neuro-Oncology (J.H.U.), Mayo Clinic, Rochester, MN 55905, USA; and Department of Radiation Oncology, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA (E.G.S.)

Radiotherapy is a component of the treatment regimen for the majority of patients with low-grade gliomas. Therefore, the effect of radiotherapy on the long-term cognitive performance of these patients is a major concern. This article reviews the neurocognitive effects of radiotherapy on patients with low-grade gliomas. The weight of evidence suggests only sporadic, limited neurocognitive damage from focal radiotherapy at the doses usually prescribed for low-grade gliomas. Neuro-Oncology 5, 161–167, 2003 (Posted to Neuro-Oncology [serial online], Doc. 02-043, April 8, 2003. URL http://neuro-oncology.mc.duke.edu; DOI: 10.1215/S1152 8517 02 00043 1)

The role of cranial radiotherapy in the management of low-grade gliomas has generated much controversy in the neuro-oncology community (Bahary et al., 1996; Janny et al., 1994; Leighton et al., 1997; Nicolato et al., 1995; Philippon et al., 1993; Piepmeier, 1987; Piepmeier et al., 1996; Shaw et al., 1989; Shibamoto et al., 1993; Westergaard et al., 1993). This controversy continues even after the reporting of 3 prospective, randomized phase 3 clinical trials (Karim et al., 1996, 2002; Shaw et al., 2002). Part of this controversy stems from concerns about potential morbidity after cranial radiotherapy. Because of their longer progression-free survival, patients with low-grade glioma may be more likely to experience neurocognitive deficits from radiotherapy compared with patients who harbor more aggressive brain tumors. Confounding any analyses of neurocognitive function are factors such as surgery, chemotherapy, tumor characteristics (location, lesion size, etc.), tumor progression, concurrent medical illnesses, neurologic comorbidity, and medications that can contribute to neurocognitive deficits. This article focuses on the literature regarding the neurocognitive effects of radiotherapy on patients with low-grade gliomas, although there is also a limited review of the neurocognitive impact of surgery, chemotherapy, and the tumor itself.

Literature Review

Prospective Trials

As noted above, the effect of radiotherapy on long-term cognitive performance of patients treated for intracranial neoplasms is a major concern. Data from the North Central Cancer Treatment Group support the findings of a limited impact of radiation and chemotherapy on neurocognition in patients with high-grade glioma over time (Taylor et al., 1998). Taylor and colleagues reviewed the records of 701 high-grade brain tumor patients receiving radiotherapy and chemotherapy on 2 consecutive prospective randomized treatment trials of the North Central Cancer Treatment Group (Buckner et al., 2001; Dinapoli et al., 1993). Collected data included the Folstein mini-mental status exam (MMSE), a well-validated screening test for dementia and cognitive impairment (Folstein et al., 1975; Galasko et al., 1990; Salmon et al., 1990; Tangalos et al., 1996; Tombaugh and McIntyre, 1992).
Serial MMSE scores, Eastern Cooperative Oncology Group performance scores, and tumor status recorded at baseline and at 6, 12, 18, and 24 months were analyzed to assess cognitive and physical function over time. No statistically significant increase in the percentage of patients experiencing a significant decrease (change of 4 or more points) in their MMSE scores over time was found. By contrast, there was a significant decline in MMSE scores for those patients with tumor progression compared to the patients without tumor progression \((P = 0.0006\) at 6 months and \(P = 0.0046\) at 12 months). In their conclusion, the authors noted that factors such as older age, poorer performance score, and subclinical tumor progression were the most significant factors in those patients who did demonstrate a significant cognitive decline.

Neurocognitive deficits from radiotherapy can take years to develop. One inherent weakness of the study by Taylor and associates (1998) is the short survival of patients with high-grade gliomas. Only 8.3% of the study participants were alive without progression at 24 months. With such a short median survival and time to progression, the patients may not have had enough time to "develop" late radiation neurotoxicity after receiving radiotherapy (Kramer, 1968; Kramer et al., 1972; Marks et al., 1981; Sheline et al., 1980).

More recently, Brown and colleagues (2001) reviewed the cognitive performance data collected prospectively in low-grade glioma patients, in which the median time-to-progression and survival were 5.5 and 8.4 years, respectively. This prospective clinical trial randomized 203 eligible/analyzable adult patients with supratentorial low-grade gliomas to low-dose \((50.4 \text{ Gy/28 fractions})\) or high-dose \((64.8 \text{ Gy/36 fractions})\) localized radiation therapy (Shaw et al., 2002). MMSE scores and neurologic function scores (a functional scoring system focusing on neurological status) recorded at baseline and at each study evaluation were analyzed to assess cognitive and physical function over time. A loss or gain of more than 3 points in MMSE was defined as clinically significant (Tangalos et al., 1996). The median MMSE score at baseline was 29. Median follow-up was 7.4 years in the 101 patients still alive. The more than 30% of patients alive without progression at 10 years had "sufficient time" to develop neurocognitive deficits, since most cases of late radiation neurotoxicity occur within 5 years (Kramer, 1968; Kramer et al., 1972; Marks et al., 1981; Sheline et al., 1980). The percentages of patients without tumor progression who experienced significant deterioration of their MMSE scores from baseline at years 1, 2, and 5 were 8.2%, 4.6%, and 5.3%, respectively. In contrast, the majority of patients with an abnormal baseline MMSE score (<27) experienced significant gains (59%, 50%, and 67% at years 1, 2, and 5, respectively). Although these results suggest there was no obvious cognitive decline in this patient group, subtle alterations in memory, personality, or intelligence may have occurred that were not measurable by the MMSE but might have been noted by more extensive neuropsychological testing.

A subset of 19 patients entered during the early years of the above-mentioned intergroup trial did complete a battery of neuropsychological tests at Mayo Clinic before and for up to 5 years after completing radiotherapy. No significant loss of intellectual, new learning, or memory function was found for the 2 dose groups after radiotherapy (Hammack et al., 1995).

Armstrong and colleagues (2000) conducted prospective, comprehensive, longitudinal neuropsychological studies on 20 adult patients with low-grade primary brain tumors (majority low-grade gliomas) treated with radiotherapy. The median dose of the focal radiotherapy was 54 Gy (range \(46–63 \text{ Gy}\)). The extensive test battery (a 3- to 4-h session) was performed at baseline (after surgery and before irradiation); at 3, 6, and 12 months; and up to 3 years after radiotherapy. Additionally, 24 healthy controls were matched with the brain study patients by age, education, and hand dominance for the purposes of baseline analyses. Patients demonstrated normal verbal memory (retention after interference) at baseline, decrement at 3 months, and then rebound and recovery in verbal retrieval at 1 year. Visual memory deficits (learning and retrieval after interference) were noted at baseline (before radiation), with recovery up to 1 year after radiotherapy. No changes over time were observed in other neurocognitive tests or in fatigue or mood measures. These results confirmed the authors' previous findings of an initial decrement followed by a rebound during the early-delayed period (Armstrong et al., 1993, 1995). The authors proposed that these temporary deficits were consistent with demyelination followed by remyelination. The authors also postulated that the improvement in visual learning and retrieval was due to the beneficial effects of the radiation treatments on the tumor. Metabolic positron emission tomography studies have demonstrated a treatment-related decrease in tumor metabolism correlating closely with increases in normal brain metabolism (Wang et al., 1996).

A further update by Armstrong and associates increased the number of patients to 26. The length of the prospective neuropsychological follow-up was also increased, with 9 patients undergoing neurocognitive testing 6 years after radiotherapy. Seven of the 37 neuropsychological indices showed improvement over the 6 years. Selective cognitive declines (in visual memory) emerged only at 5 years. It was hypothesized that the decline at year 5 was based on the sensitivity of the hippocampal memory system to late-delayed effects. The authors also noted that the selectivity of the cognitive decline was evidence that widespread cognitive impairment does not precipitously develop after focal radiotherapy (Armstrong et al., 2002).

Vigliani and associates (1996) conducted a prospective neuropsychological study of 17 patients who underwent conventional focal radiotherapy \((54–55.8 \text{ Gy delivered in 1.8-Gy fractions})\) for a low-grade glioma or a good-prognosis anaplastic glioma. A control population of 14 patients with low-grade gliomas who did not receive radiotherapy also underwent a battery of neuropsychological tests (Stroop Color Word Test, Wechsler Adult Intelligence Scale, Reaction Time, Verbal Span, Visual Span, Raven Progressive Matrices, Wechsler Memory Scale, Recall Rey-Osterrieth Complex Figure)
perception, memory, attention, and executive control. Performance of low-grade glioma patients on tests involving earlier. Neuropsychological testing revealed poor patients, 104 had received radiation therapy 1 to 22 years patients with low-grade hematological malignancies and glioma patients (N = 195) were compared to 100 control patients with low-grade gliomas without signs of tumor recurrence. The patients were also tested psychologically to assess their actual affective status by using the Profile of Mood States exam. Twenty of the adult patients had been treated with early focal radiotherapy (45–63 Gy), and the other 21 patients had undergone surgery or biopsy only. Nineteen patients with low-grade hematological malignancies (not receiving chemotherapy and without CNS involvement) served as control subjects. None of the survivors had significant neurological impairment, and the Karnofsky index for them was at least 70. However, more specific examinations of cognitive functions and the affective status (Profile of Mood States) indicated that, compared to the control subjects, the patients with low-grade gliomas had significantly more cognitive disturbances and suffered more frequently from fatigue and depressed moods. The 2 groups with low-grade gliomas, on the other hand, did not differ significantly on any of these measures. The lack of neurocognitive deficits caused by radiotherapy in this series was attributed to the treatment of patients with focal radiotherapy and not whole-brain radiotherapy (WBRT). The authors concluded that focal radiotherapy had no negative impact on the neurologic, functional, cognitive, and affective status of these low-grade glioma patients.

Klein, Taphoorn, and colleagues later extended their neuropsychological testing of low-grade glioma patients (Klein et al., 2001). Histologically confirmed low-grade glioma patients (N = 195) were compared to 100 control patients with low-grade hematological malignancies and 195 healthy controls. Of the 195 low-grade glioma patients, 104 had received radiation therapy 1 to 22 years earlier. Neuropsychological testing revealed poor performance of low-grade glioma patients on tests involving perception, memory, attention, and executive control when compared to control patients with low-grade malignancies and even worse performance when compared to healthy controls. When only low-grade glioma patients were analyzed as a group, radiation therapy did not seem to have a significant impact on the scores of the neuropsychological tests. The authors did find antiepileptic use predictive of deficits in attention and executive function.

North and colleagues reviewed 77 patients with supratentorial grade I or II astrocytomas treated at Johns Hopkins Hospital (North et al., 1990). Sixty-six patients received postoperative radiation therapy to a dose of 5040 to 5580 cGy. Quality of life (QOL) was determined at 2 points in time, 1 to 2 years postoperatively and at last follow-up (2–12 years postoperatively). There was no correlation between neurocognitive deterioration and radiotherapy. None of the adult survivors had “significant memory loss or decreased mentation” after radiotherapy.

Whole Brain versus Focal Field Irradiation

WBRT is well known to cause neurocognitive deficits, especially when large fraction sizes are used (DeAngelis et al., 1989). In contrast, some have stated that the risks of cognitive dysfunction after focal conventional radiotherapy are “virtually absent” (Keime-Guibert et al., 1998). Kleinberg and associates (1993) reviewed 30 adult long-term disease-free survivors of intracranial gliomas after radiotherapy (54–66 Gy) and chemotherapy (83% of patients). Sixteen patients received partial brain irradiation only, 12 had whole-brain irradiation with a partial brain boost, and 2 had whole-brain irradiation only. The authors found that long-term glioma survivors maintained a relatively good performance status in the absence of recurrence and did not experience a progressive decline in neuropsychologic function after completion of cranial irradiation. Additionally, they found that patients treated with partial brain irradiation had a higher and more stable performance status, better memory function, and superior employment history compared to those patients treated with WBRT.

These results are consistent with the experience at the University of Helsinki (Surma-aho et al., 2001). Surma-aho and colleagues reviewed a cohort of 160 patients who underwent surgery for low-grade gliomas. At a mean follow-up time of 7 years, 28 of the 101 patients who had postoperative irradiation (and no second surgery or chemotherapy) were still alive and eligible for MRI and neuropsychological study (Digit Span, Similarities, Block Design, and Digit Symbol subtests from the Wechsler Adult Intelligence Scale, and a Modified Benton Visual Retention Test). The median total postoperative dose was 60 Gy. The majority of the patients received whole-brain irradiation to 40 Gy followed by a boost of 20 to 28 Gy. Of the 39 patients who did not have radiotherapy, second surgery, or chemotherapy, 23 were alive and eligible at a mean of 10 years. Confounding the analyses, there was an imbalance between the 2 groups, with the surgery-only group having significantly more patients with “grade 1 gliomas.” The neuropsychological testing did reveal poorer memory performances in the postop-
erative irradiation group compared to the surgery-alone group.

Gregor and associates (1996) reviewed their experience at Western General Hospital in Edinburgh for adult brain tumor patients surviving in clinical and radiological remission more than 4 years following irradiation. The 30 patients identified represented all but 1 long-term survivor treated with radiotherapy in their department between 1971 and 1990. All 30 patients underwent clinical examination, CT/MRI scan, and neuropsychological testing (National Adult Reading Test, Wechsler Adult Intelligence Scale, Trail-Making Test, Complex Figure Test, and Hospital Anxiety and Depression Scale). Sixteen patients treated from 1971 until 1986 received whole-brain irradiation (average dose 43.2 Gy in 21.8 fractions), while focal irradiation (average dose 54.1 Gy in 30 fractions) was used (because of a departmental treatment policy change) for the 14 patients treated after 1986. The 2 groups were similar in age, initial tumor type, premorbid IQ estimates, and surgical treatment, but the WBRT group showed more evidence of neuropsychological impairment than the focal radiotherapy group, even though higher doses of radiation were delivered in the focal radiotherapy group. There were significantly lower median scores in tests of visuospatial organization, visual memory, and complex information in the WBRT group. The chance of developing significant neuropsychological impairment was 7 times greater in the WBRT group than in the focal radiotherapy group. Multivariate analysis by logistic regression confirmed WBRT as the only independent predictor of neuropsychological impairment.

Asai and colleagues reviewed 91 patients with brain tumors treated by resection followed by postoperative radiotherapy (Asai et al., 1987, 1989). Additionally, some of the patients received chemotherapy. They found a significantly higher incidence of radiation-induced brain atrophy and dementia in the patients treated with WBRT compared to those treated with focal radiotherapy. The authors recommended focal radiotherapy as opposed to WBRT whenever possible.

Dose of Radiotherapy

Cognitive performance data collected on an intergroup trial randomizing adult patients with supratentorial low-grade gliomas to low-dose (50.4 Gy/28 fractions) or high-dose (64.8 Gy/36 fractions) focal radiation therapy was reviewed by Brown and associates (2001). In their analyses, Brown et al. did not find any relationship between MMSE deterioration and the dose of radiation. Kiebert and colleagues (1998) reviewed the European Organization for Research and Treatment of Cancer phase 3 study comparing high-dose (59.4 Gy in 6.3 weeks) versus low-dose (45 Gy in 5 weeks) radiotherapy with conventional techniques in patients with low-grade cerebral gliomas. A QOL questionnaire, consisting of 47 items assessing a range of physical, psychological, social, and symptom domains, was included in the trial to measure the impact of treatment over time. Patients who received high-dose radiotherapy tended to report lower levels of functioning and more symptom burden following completion of radiotherapy compared to the patients who received low-dose radiotherapy. These differences between the treatment arms were statistically significant for fatigue/malaise and insomnia immediately after radiotherapy and in leisure time and emotional functioning at 7 to 15 months after randomization.

Radiotherapy Fraction Size

DeAngelis and associates (1989) reported on 12 patients with brain metastases who developed delayed complications of WBRT (8 also underwent surgical resection). The incidence of WBRT-induced dementia was 1.9% to 5.1% in the 2 populations reviewed. Although the total dose of WBRT was only 2500 to 3900 cGy, daily fractions of 300 to 600 cGy were used in these patients. The authors noted that large daily fraction sizes predispose patients to delayed neurologic toxicity, and they recommended more protracted schedules (smaller fraction sizes) to improve the safety and efficacy of WBRT for “good-risk” patients with brain metastases.

Although Klein and colleagues did not find radiotherapy detrimental for the neurocognition of low-grade patients as a group, they did find clinically significant reductions in long-term memory functioning in a subset of patients receiving large fraction sizes (Klein et al., 2001). The authors concluded that the use of conventional radiotherapy delivered in fraction sizes not exceeding 200 cGy was “safe” with regard to cognitive side-effects.

Impact of Surgery

The decision to proceed immediately with surgery (biopsy or resection) when clinical and radiographic findings are consistent with a low-grade glioma is difficult and controversial. The impact of “early versus late” intervention is an important issue. Reijneveld and associates attempted to address this issue by performing a case-matched control study (Reijneveld et al., 2001). The authors recruited 24 patients suspected of having a low-grade glioma in whom treatment was deferred and 24 histologically proven low-grade glioma patients who underwent early surgery (6 were biopsy only). None of these patients received radiotherapy. Healthy control subjects were also matched. The 2 patient groups were matched for tumor laterality, use of anticonvulsants, and interval between diagnosis and testing. The QOL and cognitive status of the 3 groups were compared. The low-grade glioma patients scored worse on QOL scales than healthy control subjects. Unoperated patients with low-grade gliomas scored better on most items than patients with low-grade gliomas who underwent early surgery. Cognitive status was worse in the low-grade glioma patients than in the healthy control subjects, but again, patients with suspected low-grade glioma performed better than patients with low-grade glioma who underwent surgery. Although there is undoubtedly some selection bias for patients with more aggressive tumors to undergo intervention, this study suggested early surgical inter-
vention for low-grade gliomas patients can lead to increased risk of neurocognitive deficits and a worse QOL. These results are consistent with the findings of an earlier report from the University of Massachusetts Medical Center that found no detrimental impact on survival or QOL by deferring treatment for patients with suspected low-grade gliomas (Recht et al., 1992).

Impact of Chemotherapy

Chemotherapy is a frequently utilized modality in the treatment of patients with low-grade gliomas, albeit more commonly in the setting of recurrent disease than initial presentation. However, chemotherapy also has significant risks of acute and long-term toxicities. Chemotherapy given concurrently with radiation increases the risk of neurocognitive deficits compared to radiotherapy alone (Keime-Guibert et al., 1998). In fact, patients with non-CNS malignancies treated with chemotherapy (and without cranial radiotherapy) have been found to have an increased risk of neurocognitive impairment (Ahles et al., 2002; Brezden et al., 2000; Schagen et al., 1999; van Dam et al., 1998). A recently closed intergroup trial (study RTOG 98-02 [RTOG, 2002]) randomized “high-risk” adult patients with supratentorial low-grade gliomas between localized external beam radiation therapy (54 Gy in 30 fractions) alone or followed by 6 cycles of procarbazine/CCNU/vincristine chemotherapy. The results of this trial will provide helpful information, since it is possible the addition of chemotherapy could result in an increased incidence of neurocognitive deficits (Lesser, 2001).

Location of Tumor

Non–treatment-related factors such as location of tumor by hemisphere can be predictive factors for cognitive outcome. A recently reported trial from Duke University (Hahn et al., 2000) enrolled 68 adults with newly diagnosed malignant brain tumors on a prospective trial prior to radiotherapy. Six neuropsychologic tests were administered. In addition, QOL was measured by Karnofsky performance status and a single-item linear analogue self-assessment. Eighteen patients had left-hemisphere tumors (27%); 39 had right-hemisphere tumors (57%); and 11 had bilateral, posterior fossa, or thalamic tumors (16%). Patients with left-hemisphere tumors reported more memory problems and more depressive symptoms. They also exhibited poorer attention, were more distractible, and had poorer verbal fluency and poorer verbal learning. These results are consistent with the previously mentioned study from the Netherlands (Taphoorn et al., 1994). Taphoorn and colleagues found patients with left-hemisphere tumors to have worse concentration and cognitive abilities on neurocognitive testing compared to patients with right-hemisphere lesions. In contrast, the prospective trial by Armstrong and associates (2000) found no effect of tumor hemispheric laterality on time-dependent changes in memory after radiotherapy.

Conclusions

Some of the reservations about the use of radiation treatments for patients with low-grade glioma revolve around the potential for late neurocognitive side effects in a group of patients with often relatively indolent tumors and longer life expectancy. Although many of the retrospective and prospective studies outlined in this review have some limitations (small sample size, multiple confounding factors, etc.), taken as a whole they do suggest that the increased time to tumor progression afforded by radiation need not come at the price of neurocognitive function. A consistent finding in many of the studies is that the amount of radiation given, both volume and dose, is an important determinant of neurocognitive function, underscoring the importance of appropriate radiation targeting and dosing. In the past, radiation treatments were often delivered with large fraction size or higher total doses of radiation (60 Gy or higher). Additionally, whole-brain fields, or large partial-brain fields, were employed with simple (minimal shaping, parallel opposed pair) beam arrangements. As a consequence, large volumes of uninvolved brain were irradiated with high doses of radiation, with subsequent significant neurocognitive side effects years later. With improved imaging, three-dimensional treatment-planning computer software, and sophisticated beam-shaping devices (multi-leaf collimators), it is now possible to precisely target and irradiate partial volumes within the brain. By restricting the high-dose volume to the MRI-delineated tumor volume through the use of multiple, overlapping, conformal-shaped fields, the potential neurocognitive side effects are minimized. Furthermore, reservations about the potential neurotoxicity of radiation should also be tempered by the observation that radiation significantly delays time to tumor progression, which, in turn, delays the cognitive decline associated with tumor progression.

Therefore, concerns about significant neurotoxicity from focal, conventionally fractionated radiotherapy should not prohibit proceeding if clinically indicated. With further advances in radiotherapy, such as intensity-modulated radiotherapy and fractionated linear accelerator-based radiosurgery, it is possible to provide even more precise radiotherapy than has been delivered in the recent past (Cardinale et al., 1998; Khoo et al., 1999; Singh et al., 2001). By sparing more brain from high-dose radiotherapy, there is the potential to decrease even further the risks of long-term neurocognitive deficits.
References


Brown et al.: Neuro-cognitive effects of radiation therapy


