Medical Policy

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(See policy history boxes for previous effective dates)

Title: Intensity Modulated Radiation Therapy (IMRT): Central Nervous System Tumors

Description/Background

RADIOTHERAPY TECHNIQUES

Radiation therapy may be administered externally (ie, a beam of radiation is directed into the body) or internally (ie, a radioactive source is placed inside the body, near a tumor). External radiotherapy (RT) techniques include "conventional" or 2-dimensional (2D) RT, 3-dimensional (3D) conformal RT, and intensity-modulated radiation therapy (IMRT).

Conventional External Beam Radiotherapy

Methods to plan and deliver RT have evolved in ways that permit more precise targeting of tumors with complex geometries. Conventional 2D treatment planning utilizes X-ray films to guide and position radiation beams.[1] Bony landmarks visualized on X-ray are used to locate a tumor and direct the radiation beams. The radiation is typically of uniform intensity.

Three-Dimensional Conformal Radiotherapy

Radiation treatment planning has evolved to use 3D images, usually from computed tomography (CT) scans, to more precisely delineate the boundaries of the tumor and to discriminate tumor tissue from adjacent normal tissue and nearby organs at risk for radiation damage. Three-dimensional conformal RT (3D-CRT) involves initially scanning the patient in the position that will be used for the radiation treatment.[1] The tumor target and surrounding normal organs are then outlined in 3D on the scan. Computer software assists in determining the orientation of radiation beams and the amount of radiation the tumor and normal tissues receive to ensure coverage of the entire tumor in order to minimize radiation exposure for at risk normal tissue and nearby organs. Other imaging techniques and devices such as multileaf collimators (MLCs) may be used to "shape" the radiation beams. Methods have also been developed to position the patient and the radiation portal reproducibly for each fraction and to immobilize the patient, thus maintaining consistent beam axes across treatment sessions.

Intensity-Modulated Radiotherapy
IMRT is the more recent development in external radiation. Treatment planning and delivery are more complex, time-consuming, and labor-intensive for IMRT than for 3D-CRT. Similar to 3D-CRT, the tumor and surrounding normal organs are outlined in 3D by a scan and multiple radiation beams are positioned around the patient for radiation delivery.[1] In IMRT, radiation beams are divided into a grid-like pattern, separating a single beam into many smaller "beamlets". Specialized computer software allows for “inverse” treatment planning. The radiation oncologist delineates the target on each slice of a CT scan and specifies the target’s prescribed radiation dose, acceptable limits of dose heterogeneity within the target volume, adjacent normal tissue volumes to avoid, and acceptable dose limits within the normal tissues. Based on these parameters and a digitally reconstructed radiographic image of the tumor and surrounding tissues and organs at risk, computer software optimizes the location, shape and intensities of the beams ports, to achieve the treatment plan’s goals.

Increased conformality may permit escalated tumor doses without increasing normal tissue toxicity and is proposed to improve local tumor control, with decreased exposure to surrounding, normal tissues, potentially reducing acute and late radiation toxicities. Better dose homogeneity within the target may also improve local tumor control by avoiding underdosing within the tumor and may decrease toxicity by avoiding overdosing.

Other advanced techniques may further improve RT treatment by improving dose distribution. These techniques are considered variations of IMRT. Volumetric modulated arc therapy delivers radiation from a continuous rotation of the radiation source. The principal advantage of volumetric modulated arc therapy is greater efficiency in treatment delivery time, reducing radiation exposure and improving target radiation delivery due to less patient motion. Image-guided RT involves the incorporation of imaging before and/or during treatment to more precisely deliver RT to the target volume.

Regulatory Status

In general, IMRT systems include intensity modulators, which control, block, or filter the intensity of radiation; and RT planning systems, which plan the radiation dose to be delivered.

A number of intensity modulators have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. Intensity modulators include the Innocure Intensity Modulating Radiation Therapy Compensators (Innocure) and Decimal Tissue Compensator (Southeastern Radiation Products), cleared in 2006. FDA product code: IXI. Intensity modulators may be added to standard linear accelerators to deliver IMRT when used with proper treatment planning systems.

Radiotherapy treatment planning systems have also been cleared for marketing by FDA through the 510(k) process. They include the Prowess Panther (Prowess) in 2003, TiGRT (LinaTech) in 2009, and the Ray Dose (RaySearch Laboratories). FDA product code: MUJ.

Fully integrated IMRT systems also are available. These devices are customizable and support all stages of IMRT delivery, including planning, treatment delivery, and health record

management. One such device cleared for marketing by FDA through the 510(k) process is the Varian IMRT system (Varian Medical Systems). FDA product code: IYE.

Medical Policy Statement

Intensity-modulated radiotherapy (IMRT) may be considered established for the treatment of malignant or benign brain tumors based on the analysis of dosimetric data including comparative models if necessary.

Inclusionary and Exclusionary Guidelines

Refer to medical policy statement.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

77301 77338 77385 77386 77387 G6015
G6016

Other codes (investigational, not medically necessary, etc.):

N/A

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The

quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Multiple-dose planning studies generate 3D-CRT and IMRT treatment plans from the same scans, and then compare predicted dose distributions within the target area and adjacent organs. Results of such planning studies have shown that IMRT is better than 3D-CRT with respect to conformality to, and dose homogeneity within, the target. Results have also demonstrated that IRMT less radiation to nontarget areas. Dosimetry studies using stationary targets generally confirm these predictions. However, because patients move during treatment, dosimetry with stationary targets only approximate actual radiation doses received. Based on these dosimetry studies, radiation oncologists expect IMRT to improve treatment outcomes compared with those of 3D-CRT.

Comparative studies of radiation-induced adverse effects from IMRT versus alternative radiation delivery would constitute definitive evidence in establishing the benefit of IMRT. Single-arm series of IMRT can give some insights into the potential for benefit, particularly if an adverse effect that is expected to occur at high rates is shown to decrease by a large amount. Studies of treatment benefit are also important to establish that IMRT is at least as good as other types of delivery, but, absent such comparative trials, it is likely that benefit from IMRT is at least as good as with other types of delivery.

In general, when the indication for IMRT is to avoid radiation to sensitive areas, dosimetry studies have been considered sufficient evidence to demonstrate that harm would be avoided by using IMRT. For other IMRT indications, such as using IMRT to provide better tumor control, comparative studies of health outcomes are needed to demonstrate such a benefit.

MALIGNANT BRAIN TUMORS

Clinical Context and Therapy Purpose

The purpose of IMRT in individuals who have malignant brain tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with malignant brain tumors.

Interventions

The therapy being considered is IMRT.

Radiotherapy (RT) is an integral component of treating many brain tumors, both benign and malignant. IMRT is a method that allows adequate radiation to the tumor while minimizing the dose to surrounding normal tissues and critical structures. IMRT also allows additional

radiation to penetrate specific anatomic areas simultaneously, delivering radiation at a larger target volume.

Comparators
The following therapy is currently being used to treat malignant brain tumors: 3D-CRT.

Outcomes
The general outcomes of interest are overall survival (OS), disease-specific survival (DSS), reductions in symptoms, functional outcomes, and treatment-related adverse events. A proposed benefit of IMRT is to reduce toxicity to adjacent structures, allowing dose escalation to the target area and fewer breaks in treatment courses due to a reduction in side effects. However, this may come with a loss of locoregional control and OS due to factors discussed above. The time frame for outcome measures varies from short-term management of toxicity and symptoms to long-term procedure-related complications, cancer progression or recurrence, and OS.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Systematic Reviews
Amelio et al (2010) conducted a systematic review on the clinical and technical issues of using IMRT in newly diagnosed glioblastoma multiforme.[2] Articles were selected were through December 2009 and included 17 studies (9 related to dosimetric data and technical considerations, 7 to clinical results, and 1 to both dosimetric and clinical results) for a total of 204 treated patients and 148 patient datasets used in planning studies. No randomized controlled studies were identified, and a meta-analysis was not performed.

For the 6 articles related to planning studies that compared 3D-CRT with IMRT, the report by Fuller et al (2007) showed a noticeable difference between 3D-CRT and IMRT for the planning target volume (PTV; 13% benefit in V95 [volume that received 95% of the prescribed dose] from IMRT; $p<0.001$)[3]; the remaining studies suggested that IMRT and 3D-CRT provide similar PTV coverage, with differences between 0% and 1%. Target dose conformity was found to be improved with IMRT. The organs at risk in the studies typically were the brainstem, optic chiasm, optic nerves, lens, and retina. In general, IMRT provided better sparing of the organs at risk than 3D-CRT but with considerable variation from study to study.

Of the 8 studies that included clinical results, 3 were retrospective; 1 was a prospective phase 1 study, and 4 were prospective phase 2 single-institution studies. Of these 8 studies, 2 used conventional total dose and dose per fraction, 2 used a hypofractionated regimen, and the

others used a hypofractionated scheme with a simultaneous integrated boost. The median follow-up ranged from 8.8 to 24 months. Almost all patients (96%) completed treatment without interruption or discontinuation due to toxicity. Acute toxicity was reported as negligible, with grade 3 adverse events observed in only 2 studies at rates of 7% and 12%. Grade 4 toxicity was recorded in only 1 series, with an absolute rate of 3%. Data for late toxicities were available in 6 of 8 studies, with 1 recording grade 4 adverse events with an incidence of 20%. One- and 2-year OS rates varied between 30% and 81.9% and between 0% and 55.6%, respectively. When OS was reported as a median time it ranged from 7 to 24 months. Progression-free survival rates ranged from 0% to 71.4% at 1 year and from 0% to 53.6% at 2 years. The median progression-free survival ranged from 2.5 to 12 months.

Reviewers also conducted a comprehensive qualitative comparison using data reported in the literature on similar non-IMRT clinical studies. The planning comparisons revealed that 3D-CRT and IMRT provided similar results in terms of target coverage. IMRT was somewhat better than 3D-CRT in reducing the maximum dose delivered to the organs at risk-although the extent varied by case. IMRT was also better than 3D-CRT when it came to dose conformity and sparing of the healthy brain tissue at medium to low doses; there were no aspects where IMRT performed worse than 3D-CRT.

The systematic review was limited by a number of factors: there was an absence of comparative studies with clinical outcomes; all studies were small in size, from a single institution; most patients (53%) were retrospectively analyzed; and chemotherapy administration varied across studies.

Dose-Planning Studies

MacDonald et al (2007) compared the dosimetry of IMRT and 3D-CRT in 20 patients treated for high-grade glioma.[4] Prescription dose and normal-tissue constraints were identical for the 3D-CRT and IMRT treatment plans. The IMRT plan yielded superior target coverage as compared with the 3D-CRT plan. The IMRT plan reduced the percent volume of brainstem receiving a dose greater than 45 gray (Gy) by 31% (p=.004) and the percent volume of brain receiving a dose greater than 18 Gy, 24 Gy, and 45 Gy by 10% (p=.059), 14% (p=.015), and 40% (p<.001), respectively. With IMRT, the percent volume of optic chiasm receiving more than 45 Gy was reduced by 30.4% (p=.047). Compared with 3D-CRT, IMRT significantly increased tumor control probability (p<.001) and lowered the normal-tissue complication probability for brain and brain stem (p<.033).

Narayana et al (2006) compared IMRT treatment plans with 3D plans performed in 20 patients of a case series of 58 patients.[5] Regardless of tumor location, IMRT did not improve planning target volume (PTV)compared with 3D planning. However, IMRT decreased the maximum dose to the spinal cord, optic nerves, and eye by 16%, 7%, and 15%, respectively.

Nonrandomized Comparison Studies

Paulsson et al (2014) compared treatment failure rates in glioblastoma patients with differing target margins (the size of the region between tumor and edge of the PTV).[6] In 161 patients, treatment margins were not associated with treatment failure. There was no difference in treatment failure rates between IMRT and 3D-CRT.

A large cohort study conducted by Xiang et al that included >450,000 patients with cancer (of which 12,143 had brain or central nervous system cancer) compared the risk of secondary tumors following treatment with IMRT and 3D-CRT across cancer types. After a mean 5 years follow-up, multivariate, matched analysis showed no difference in risk of secondary cancers between IMRT and 3D-CRT (OR 1.00, 95% CI 0.98 to 1.03). These results were consistent when limited to patients who had not received chemotherapy (OR 1.01, 95% CI 0.96 to 1.06).[7]

Section Summary: Malignant Brain Tumors
Dosimetry studies have demonstrated lower radiation exposure to organs at risk with IMRT treatment plans than with 3D-CRT treatment plans. The evidence appears to be consistent in supporting lower neurotoxicity associated with IMRT. No conclusions can be made about the efficacy of IMRT compared with conventional RT.

BENIGN BRAIN TUMORS

Clinical Context and Therapy Purpose
The purpose of IMRT in individuals who have benign brain tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

For benign and low-grade brain tumors, gross total resection remains the primary goal. However, RT may be used in select cases, such as when total resection is not possible, when a more conservative surgical approach may be necessary to achieve long-term treatment goals, and when atypical tumors may need RT even after gross total resection to reduce the risk of local recurrence. Therefore, RT, either definitive or in the postoperative adjuvant setting, remains an integral component in the management of residual, recurrent, and/or progressive benign and low-grade brain tumors for maximizing local control.8

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with benign brain tumors.

Interventions
The therapy being considered is IMRT.

Radiotherapy is an integral component of treating many brain tumors, both benign and malignant. IMRT is a method that allows adequate radiation to the tumor while minimizing the dose to surrounding normal tissues and critical structures. IMRT also allows additional radiation to penetrate specific anatomic areas simultaneously, delivering radiation at a larger target volume.

Comparators
The following therapy is currently being used to treat benign brain tumors: 3D-CRT.

Outcomes
The general outcomes of interest are OS, DSS, functional outcomes, and treatment-related adverse events. A proposed benefit of IMRT is to reduce toxicity to adjacent structures,

allowing dose escalation to the target area and fewer breaks in treatment courses due to a reduction in side effects. However, this may come with a loss of locoregional control and OS due to factors discussed above. The time frame for outcome measures varies from short-term management of toxicity and symptoms to long-term procedure-related complications, cancer progression or recurrence, and OS.

Study Selection Criteria
See information under the first indication.

REVIEW OF EVIDENCE

Case Series
The evidence for use of IMRT in patients with benign brain tumors consists mostly of case series. Previously discussed dosimetry studies, which evaluated patients with malignant brain tumors, should be generalizable to patients with benign tumors.

Milker-Zabel et al (2007) reported on results of treatment of complex-shaped meningiomas at the skull base with IMRT.[9] Ninety-four patients received RT as primary treatment (n=26), for residual disease after surgery (n=14), or after local recurrence (n=54). Tumor histology, classified using World Health Organization, was grade 1 in 54.3%, grade 2 in 9.6%, and grade 3 in 4.2%. Median follow-up was 4.4 years. The overall local tumor control rate was 93.6%. After IMRT, 69 patients had stable disease (by computed tomography [CT] or magnetic resonance imaging [MRI]), and 19 had a tumor volume reduction. Six patients had local tumor progression on MRI at a median of 22.3 months after IMRT. In 39.8% of patients, preexisting neurologic deficits improved. Treatment-induced loss of vision was seen in 1 of 53 re-irradiated patients with a grade 3 meningioma 9 months after retreatment with IMRT.

Mackley et al (2007) reported on outcomes of treating pituitary adenomas with IMRT.[10] A retrospective chart review was conducted on 34 patients treated between 1998 and 2003. Median follow-up was 42.5 months. Radiographic local control was 89% and, among patients with secretory tumors, 100% had a biochemical response. One patient required salvage surgery for disease progression, resulting in a clinical progression-free survival of 97%. One patient who received more than 46 Gy experienced optic neuropathy 8 months after radiation.

Sajja et al (2005) reported the outcomes of 35 patients with 37 meningiomas treated with IMRT.[11] Tumor histology was benign in 35 and atypical in 2 tumors. The median CT with MRI follow-up was 19.1 months (range, 6.4-62.4 months). Fifty-four percent of the meningiomas had received surgery or radiosurgery before IMRT, and 46% were treated with IMRT, primarily after a diagnosis was established by CT or MRI. Three patients had local failure after treatment. No long-term complications from IMRT were documented among the 35 patients.

Rogers et al (2020) published a more recent case series that included 57 patients with new or recurrent meningioma (WHO Grade 2 or 3) treated with 60 Gy high dose and 54 Gy low dose IMRT following resection. Three-year PFS was 58.8% and overall survival at a mean follow-up of 4 years was 78.6%. Serious adverse events were rare (1.9%).[12]

Section Summary: Benign Brain Tumors
The evidence on IMRT for treating benign brain tumors includes case series. Case series results have consistently shown low radiation toxicity but have not demonstrated better tumor control or improved survival with IMRT vs other RT techniques. The dose-planning studies evaluating IMRT in patients with malignant tumors should generalize to patients with benign brain tumors because the benefit of minimizing radiation toxicity to sensitive brain areas is identical.

BRAIN METASTASES

Clinical Context and Therapy Purpose
The purpose of IMRT to avoid hippocampal exposure in individuals who have brain metastases is to provide a treatment option that is an alternative to or an improvement on existing therapies. Intensity-modulated radiotherapy can deliver additional radiation boosts to specific metastases concurrent with whole-brain radiotherapy (WBRT). Clinicians have treated patients using this RT technique rather than treating them separately with WBRT and stereotactic radiosurgery (SRS), the latter having been shown to be more effective than WBRT alone in an RCT.

Brain metastases occur in up to 40% of adults with cancer and can shorten survival and detract from the quality of life. Many patients who develop brain metastases will die of progressive intracranial disease. Among patients with good performance status, controlled extracranial disease, favorable prognostic features, and a solitary brain metastasis, randomized studies have shown that surgical excision followed by whole-brain radiotherapy (WBRT) prolongs survival.[4] Stereotactic radiosurgery can replace surgery in certain circumstances, delivering high single doses to discrete metastases.[4] For bulky cerebral metastases, level 1 evidence has also shown that delivering a higher radiation dose with an SRS boost is beneficial in addition to standard WBRT. The use of a concomitant boost with IMRT during WBRT has been attempted to improve overall local tumor control without the use of SRS to avoid additional planned radiation after WBRT ("phase 2" or SRS) and its additional labor and expense.[4] Another indication for the use of IMRT in WBRT is to avoid radiation exposure to the hippocampus. It is thought that avoiding the hippocampus may minimize cognitive decline associated with WBRT.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with brain metastases.

Interventions
The therapy being considered is IMRT to avoid hippocampal exposure.

Comparators
The following therapy is currently being used to treat benign brain metastases: WBRT.

Outcomes
The general outcomes of interest are OS, DSS, functional outcomes, and treatment-related adverse events. A proposed benefit of IMRT is to reduce toxicity to adjacent structures,

allowing dose escalation to the target area and fewer breaks in treatment courses due to a reduction in side effects. However, this may come with a loss of locoregional control and OS due to factors discussed above. The time frame for outcome measures varies from short-term management of toxicity and symptoms to long-term procedure-related complications, cancer progression or recurrence, and OS.

Study Selection Criteria
See information under the first indication.

REVIEW OF EVIDENCE

Randomized Controlled Studies
Dosimetry studies have previously established techniques that avoided radiation exposure to this region but still provided coverage and conformality to the remaining brain. Dosimetry studies alone have not been sufficient to establish IMRT as a standard treatment because the toxic effects of radiation on the hippocampus are less well established.

Brown et al (2020) reported results from a phase III trial of 518 patients with brain metastases that assessed the comparative effectiveness of hippocampal-avoiding WBRT (HA-WBRT) using IMRT with conventional WBRT; both groups received memantine.[13] Study inclusion criteria required that patients have no brain metastases outside a 5-mm margin around either hippocampus (Table 1). The primary outcome was time to loss of cognitive function, though OS and toxicity were also reported. After a mean 8-months follow-up, HA-WBRT was associated with a reduced loss of cognitive function (adjusted HR 0.74, 95% CI 0.58 to 0.95) without any difference between groups in overall survival (HR, 1.13, 95% CI 0.90 to 1.41) (Table 2). Specifically, at 4-month follow-up, the HA-WBRT showed less loss of executive function (23.3% vs. 40.4%; p=.01), while at 6 months, there was less decline in learning (11.5% vs. 24.7%, p=.049) and memory (16.4% vs. 33.3%, p=.02) in the HA-WBRT group. At 6 months, patients in the HA-WBRT plus memantine arm reported less difficulty with remembering things (mean, 0.16 vs. 1.29; p=.01) and less difficulty speaking (mean, 20.20 vs. 0.45; p=.049) compared with the WBRT plus memantine arm. There was no difference between groups in quality of life at any time point, nor was there a difference between groups in grade 3 or higher toxicity. The study authors noted that the treatment was likely to be most effective in patients with >4 months expected survival, due to cognitive deterioration likely to occur in those with shorter expected survival. This trial indicates evidence of benefit of HA-WBRT versus WBRT on cognitive outcomes (absolute risk difference 10%) and there were no differences in toxicity, intracranial PFS, or OS.

The study has some limitations. At 4-month follow-up, only about half of the enrolled participants in both groups provided data for the individual cognitive assessments, because a large proportion of the participants had died. This was also the time point at which a clear difference emerged between groups showing a lower risk of cognitive failure in the HA-WBRT group. In addition, a significantly higher proportion of those allocated to HA-WBRT did not receive treatment 10.7% (28/261) compared to 3.1% (8/257) in the WBRT group (p=.0016). Study limitations are further described in Table 3.

Table 1. Summary of Randomized Controlled Trial Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions

					Active	Comparator
Brown et al (2020); NRG Oncology CC001 (Phase 3)[13]	US, Canada	220	2015-2018	Adults with brain metastases outside a 5-mm margin around either hippocampus; Karnofsky performance score ≥70; pathologically proven diagnosis of solid tumor malignancy. Prior resection or radiosurgery was allowed.	N=261 HA-WBRT: Bilateral hippocampal contours were manually generated on a fused thin- slice MRICT image set and expanded by 5 mm to generate the HA region + 30 Gy in 10 fractions) + memantine (5-7mg/day titrated to 20-28 mg/day)	N=257 WBRT (30 Gy in 10 fractions) + memantine (5-7mg/day titrated to 20-28 mg/day)

Gy: gray; HA: hippocampal-avoiding; MRI-CT: magnetic resonance imaging-computed tomography; WBRT: whole-brain radiotherapy .

Table 2. Summary of Key RCT Results

Study; Trial	Cognitive failure, cumulative incidence, 12 months	Overall survival	Quality of Life	Grade ≥3 adverse event
Brown et al (2020); NRG Oncology CC001 (Phase 3)[13]	N=518	N=518	N=135	N=433
HA-WBRT + memantine	117/261 (44.8%)	144/261 (55.2%)	5.34 (SD 21.80)	124/211 (58.8%)
WBRT + memantine	142/257 (55.2%)	150/257 (58.4%)	3.18 (SD 24.98)	137/222 (61.7%)
HR/Diff/OR/RR (95% CI)	Unadjusted HR 0.76 (95% CI 0.60 to 0.98)[1] Adjusted HR 0.74 (95% CI 0.58 to 0.95) ARD -0.10 (95% CI -0.19 to -0.02)	HR, 1.13 (95% CI 0.90 to1.41)	MD 2.16 (95% CI -5.73 to 10.05)[1]	RR 0.95 (95% CI 0.82 to 1.11)[1]

ARD: absolute risk difference; CI: confidence interval; HA-WBRT: hippocampal-avoiding whole body radiation; HR: hazard ratio; MD: mean difference; RCT: randomized controlled trial; RR: relative risk; SD: standard deviation.
1 Calculated estimate based on available data

Table 3. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Brown et al (2020); NRG Oncology CC001 (Phase 3)[13]		1. Due to the nature of the treatment, blinding was deemed not possible. However, assessors were blinded for the cognitive outcome.		1.The proportion of patients withdrawing from the study in the first 6 months ranged from 14% to 27%; the study protocol adjusted for missing data using imputation		3.Risk estimates were not reported for individual timepoints for the primary outcome "time to cognitive failure". Risk estimates not reported for quality of life outcome or harms

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician. 3. Blinding unclear
c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference
f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Nonrandomized Comparative Studies

Gondi et al (2014) evaluated IMRT as a method to avoid radiation exposure to the hippocampus to prevent cognitive adverse effects in patients receiving WBRT.[14] The Gondi et al (2014) study was a prospective trial with a prespecified comparison to a historical control group derived from a previously conducted clinical trial. The outcomes were standardized cognitive assessments and health-related quality of life evaluated at baseline and 2-month intervals (out to 6 months). Of 100 eligible patients, 42 patients were evaluable at 4 months; 17 patients were alive but did not have cognitive testing, and 41 had died. The mean decline in the primary cognitive end point was 7.0%, which was significantly less than the 30% decline in the historical control group ($p<.001$). Median survival in the experimental group was 6.8 months and 4.9 months in the historical control group. Although the trial results suggested that hippocampal-sparing WBRT using IMRT is associated with less cognitive decline, the historical control design adds uncertainty to the conclusion. Because the experimental group had survived longer, even though the radiation dose was intended to be equivalent to the historical control, possible unmeasured patient factors associated with better survival may have also caused less cognitive decline. The trial did not provide conclusive evidence that hippocampal-sparing IMRT causes less cognitive decline.

Case Series

A retrospective study by Zhou et al (2014) evaluated the feasibility of WBRT plus simultaneous integrated boost with IMRT for inoperable brain metastases of non-small-cell lung cancer.[15] Twenty-nine non-small-cell lung cancer patients with 87 inoperable brain metastases were included. All patients received WBRT at a dose of 40 gray (Gy) and simultaneous integrated boost with IMRT at a dose of 20 Gy concurrent with WBRT in week 4. Prior to each fraction of image-guided IMRT boost, online positioning verification and correction were used to ensure that the set-up errors were within 2 mm by cone beam CT in all patients. The 1-year intracranial control rate, local brain failure rate (BFR), and distant BFR were 63%, 14%, and 19%, respectively. The 2-year intracranial control rate, local BFR, and distant BFR were 42%, 31%, and 36%, respectively. Both the median intracranial PFS and median OS were 10 months; 6-month, 1-year, and 2-year OS rates were 66%, 41%, and 14%, respectively. Patients had better survival rates when their Score Index for Radiosurgery in Brain Metastases greater than 5, when they had fewer than 3 intracranial lesions, and when they had history of epidermal growth factor receptor–tyrosine kinase inhibitor treatment. Radiation necrosis was observed in 3 (3.5%) lesions after RT. Grades 2 and 3 cognitive impairment with grade 2 radiation leukoencephalopathy were observed in 4 (14%) patients. No dosimetric parameters were found to be associated with these late toxicities. Patients who received EGFR-TKI treatment had higher incidences of grades 2 and 3 cognitive impairment with grade 2

leukoencephalopathy. This evidence would suggest WBRT plus simultaneous integrated boost with IMRT is a tolerable treatment for NSCLC patients with inoperable brain metastases. However, the evidence does not permit conclusions about efficacy.

Section Summary: Brain Metastases
For treatment of brain metastases, IMRT has been investigated as a technique to avoid hippocampal radiation exposure when delivering WBRT and to deliver additional radiation to specific areas of the brain as a substitute for SRS. Evidence from randomized and nonrandomized studies found IMRT associated with better cognitive outcomes versus WBRT and historical controls. Evidence regarding improvements in other health outcomes is not definitive.

SUMMARY OF EVIDENCE

For individuals who have malignant brain tumors who receive intensity-modulated radiotherapy IMRT, the evidence includes dose-planning studies, nonrandomized comparison studies, and a systematic review. Relevant outcomes are overall survival (OS), disease-specific survival (DSS), morbid events, functional outcomes, and treatment-related morbidity. Study results have consistently shown low radiation toxicity but have not demonstrated better tumor control or improved survival with IMRT. Dose-planning studies have shown that IMRT delivers adequate radiation doses to tumors while simultaneously reducing radiation exposure to sensitive brain areas. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have benign brain tumors who receive IMRT, the evidence includes case series. Relevant outcomes are overall survival, disease-specific survival, functional outcomes, and treatment-related morbidity. Case series results have consistently shown low radiation toxicity but have not demonstrated better tumor control or improved survival with IMRT versus other radiotherapy techniques. It is expected that the dose-planning studies evaluating IMRT in patients with malignant tumors should generalize to patients with benign brain tumors because the benefit of minimizing radiation toxicity to sensitive brain areas is identical. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have brain tumor metastases who receive IMRT to avoid hippocampal exposure, the evidence includes a randomized trial, nonrandomized comparison studies and case series. Relevant outcomes are overall survival, disease-specific survival, functional outcomes, and treatment-related morbidity. One randomized trial and 1 prospective nonrandomized comparison study using IMRT to avoid hippocampal exposure showed less cognitive decline with IMRT than with either conventional whole brain radiotherapy (WBRT) or prespecified historical controls. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input Received Through Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, the Blue Cross Blue Shield Association received input from 3 specialty medical societies (8 reviewers) and 3 academic medical centers (3 reviewers) while their policy was under review in 2012. There was a near-uniform consensus that intensity-modulated radiotherapy (IMRT) to treat tumors of the central nervous system should be considered medically necessary, particularly for tumors in close proximity to critical structures. Reviewers considered the evidence sufficient that IMRT is regarded equally effective as 3-dimensional conformal radiotherapy; further, given the possible adverse events that could result if nearby critical structures receive toxic radiation doses (eg, blindness), IMRT dosimetric improvements should be accepted as meaningful evidence for its benefit.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network Guidelines

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines Central Nervous System Cancers (v.2.2024) support the use of highly conformal fractionated radiotherapy (RT) techniques (eg, IMRT) to "spare critical structures and uninvolved tissues."[16] When RT is given to patients with low-grade gliomas, NCCN states that "every attempt should be made to decrease the RT dose outside the target volume. This can be achieved with 3-dimensional (3 D) planning or IMRT, with improved target coverage and normal brain/critical structure sparing often shown with IMRT." The guideline also states that for high-grade gliomas, "conformal RT (CRT) techniques, which include 3D-CRT and IMRT for recommended for performing focal brain irradiation. IMRT often will provide superior dosimetric target coverage and better sparing of critical structures than 3D-CRT."

For patients with brain metastases and a prognosis of 4 months or longer, the guidelines recommend hippocampal-sparing WBRT and memantine during and after WBRT for a total of 6 months.[16] The guidelines did not include recommendations for the use of IMRT to treat high-grade tumors as well as limited or extensive metastases to the central nervous system.

American Society for Radiation Oncology

In 2022, the American Society for Radiation Oncology (ASTRO) authored a white paper on safety considerations for IMRT.[17,] Many topics related to IMRT program quality are addressed, but there is no guidance about patient selection for IMRT.

Also in 2022, the American Society for Radiation Oncology (ASTRO) authored a guideline on managing grade 2 and grade 3 diffuse glioma with isocitrate dehydrogenase

mutations.[18] Intensity-modulated radiotherapy/volumetric modulated arc therapy (VMAT) was strongly recommended in this population to reduce toxicity, especially for tumors listed near organs at risk (low quality of evidence). If IMRT/VMAT is not available, 3-D CRT is strongly recommended (moderate quality of evidence).

A 2016 model policy from ASTRO on IMRT states that IMRT is considered reasonable and medically necessary when sparing the surrounding tissue is beneficial.[19] Primary, metastatic, or benign tumors of the central nervous system (including brain, brain stem, and spinal cord) are listed as clinical indications that frequently support the use of IMRT, as well as medically necessary irradiation. The list of clinical scenarios that do not support the use of IMRT includes situations when IMRT does not offer an advantage over conventional or 3-D CRT, or in cases that are too urgent to allow for the planning that is required before administering IMRT.

American Association of Neurological Surgeons/Congress of Neurological Surgeons Joint Section on Tumors

In 2020, the American Association of Neurological Surgeons and Congress of Neurological Surgeons Joint Section on Tumors sponsored a systematic review and evidence-based clinical practice guideline update on the role of radiation therapy in the treatment of adults with newly diagnosed glioblastoma muliforme.[17] Among the 14 clinical questions that were examined, 1 question was specific for the use of IMRT: "In adult patients with newly diagnosed supratentorial glioblastoma is image-modulated RT or similar techniques as effective as standard regional RT in providing tumor control and improved survival?" The authors reviewing the clinical data concluded that: "There is no evidence that IMRT is a better RT delivering modality when compared to conventional RT in improving survival in adult patients with newly diagnosed glioblastoma. Hence, IMRT should not be preferred over the conventional RT delivery modality."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently unpublished or uncompleted trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04397679	Treatment of Adults With Newly Diagnosed Glioblastoma With Partial Brain Radiation Therapy Plus Temozolomide and Chloroquine Followed by Tumor Treating Fields Plus Temozolomide and Chloroquine -- A Pilot Study	2	Apr 2026
NCT02635009	Randomized Phase II/III Trial of Prophylactic Cranial Irradiation With or Without Hippocampal Avoidance for Small Cell Lung Cancer	418	Apr 2027
NCT04801342	Neurocognitive Outcome of Conformal Whole Brain Radiotherapy With Bilateral or Unilateral Hippocampal Avoidance Plus Memantine for Brain Metastases: A Phase II Single Blind Randomized Trial	72	Feb 2025
Unpublished			

NCT02147028	A Randomized Phase II Trial of Hippocampal Sparing Versus Conventional Whole Brain Radiotherapy After Surgical Resection or Radiosurgery in Favourable Prognosis Patients With 1-10 Brain Metastases	23	Feb 2021

NCT: national clinical trial

Government Regulations

National:

There is no national coverage determination on this topic.

Local:

Wisconsin Physicians Service Insurance Corporation – LCD Radiation Oncology Including Intensity Modulated Radiation Therapy (IMRT) (L34652)
Original Effective Date 10/01/2015
Retirement Date 04/01/2016
(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Intensity-Modulated Radiation Therapy (IMRT): Cancer of the Head and Neck or Thyroid
Intensity Modulated Radiation Therapy (IMRT) of the Abdomen, Pelvis and Chest
Intensity Modulated Radiation Therapy (IMRT) of the Breast and Lung
Intensity-Modulated Radiation Therapy (IMRT) of the Prostate

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 8/6/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/13	8/20/13	9/10/13	Joint policy established
1/1/15	10/21/14	11/3/14	Routine maintenance
7/1/16	4/19/16	4/19/16	Routine maintenance G codes added to policy
7/1/17	4/18/17	4/18/17	Routine maintenance
11/1/17	8/15/17	8/15/17	Routine maintenance
11/1/18	8/21/18	8/21/18	Routine maintenance
1/1/19	10/16/18	10/16/18	Routine maintenance: revised MPS to be more general, no exclusions; diverge from BCBSA with broader scope.
1/1/20	10/15/19		Routine maintenance
1/1/21	10/20/20		Routine maintenance
1/1/22	10/19/21		Routine maintenance Ref 17 added
1/1/23	10/18/22		Routine maintenance (ls)
1/1/24	10/17/23		Routine maintenance (jf) Vendor Managed: EviCore Add ref 17,18 and 19
1/1/25	10/15/24		Routine maintenance (jf) Vendor Managed: EviCore

Next Review Date: 4th Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: INTENSITY MODULATED RADIATION THERAPY (IMRT): CENTRAL NERVOUS SYSTEM TUMORS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria applies
BCNA (Medicare Advantage)	See Government Regulations Section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.

Attachment B
ICD10 Codes for IMRT of the Central Nervous System

ICD10 Codes	Code Description
C70.0	Malignant neoplasm of cerebral meninges
C70.1	Malignant neoplasm of spinal meninges
C70.9	Malignant neoplasm of meninges, unspecified
C71.0	Malignant neoplasm of cerebrum, except lobes and ventricles
C71.1	Malignant neoplasm of frontal lobe
C71.2	Malignant neoplasm of temporal lobe
C71.3	Malignant neoplasm of parietal lobe
C71.4	Malignant neoplasm of occipital lobe
C71.5	Malignant neoplasm of cerebral ventricle
C71.6	Malignant neoplasm of cerebellum
C71.7	Malignant neoplasm of brain stem
C71.8	Malignant neoplasm of overlapping sites of brain
C71.9	Malignant neoplasm of brain, unspecified
C72.0	Malignant neoplasm of spinal cord
C72.1	Malignant neoplasm of cauda equina
C72.20	Malignant neoplasm of unspecified olfactory nerve
C72.21	Malignant neoplasm of right olfactory nerve
C72.22	Malignant neoplasm of left olfactory nerve
C72.30	Malignant neoplasm of unspecified optic nerve
C72.31	Malignant neoplasm of right optic nerve
C72.32	Malignant neoplasm of left optic nerve
C72.40	Malignant neoplasm of unspecified acoustic nerve
C72.41	Malignant neoplasm of right acoustic nerve
C72.42	Malignant neoplasm of left acoustic nerve
C72.1	Malignant neoplasm of cauda equina
C72.20	Malignant neoplasm of unspecified olfactory nerve
C72.21	Malignant neoplasm of right olfactory nerve
C72.22	Malignant neoplasm of left olfactory nerve
C72.30	Malignant neoplasm of unspecified optic nerve
C72.31	Malignant neoplasm of right optic nerve
C72.32	Malignant neoplasm of left optic nerve
C72.40	Malignant neoplasm of unspecified acoustic nerve
C72.41	Malignant neoplasm of right acoustic nerve
C72.42	Malignant neoplasm of left acoustic nerve
C72.50	Malignant neoplasm of unspecified cranial nerve
C72.59	Malignant neoplasm of other cranial nerves
C72.9	Malignant neoplasm of central nervous system, unspecified
C79.31	Secondary malignant neoplasm of brain
C79.32	Secondary malignant neoplasm of cerebral meninges
C79.40	Secondary malignant neoplasm of unspecified part of nervous system
C79.49	Secondary malignant neoplasm of other parts of nervous system
C72.50	Malignant neoplasm of unspecified cranial nerve
C72.59	Malignant neoplasm of other cranial nerves

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ICD10 Codes for IMRT of the Central Nervous System

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