Intensity-Modulated Radiotherapy (IMRT): Central Nervous System Tumors

Policy Number: 8.01.59  Last Review: 06/2018
Origination: 06/2013  Next Review: 06/2019

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for IMRT for central nervous system tumors when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Intensity-modulated radiotherapy (IMRT) may be considered medically necessary for the treatment of tumors of the central nervous system when the tumor is in close proximity to organs at risk (brain stem, spinal cord, cochlea and eye structures including optic nerve and chiasm, lens and retina) and 3-D CRT planning is not able to meet dose volume constraints for normal tissue tolerance. (see Considerations)

When Policy Topic is not covered
Intensity modulated radiotherapy (IMRT) is considered investigational for the treatment of tumors of the CNS for all indications not meeting the criteria above.

Considerations
Organs at risk are defined as normal tissues whose radiation sensitivity may significantly influence treatment planning and/or prescribed radiation dose. These organs at risk may be particularly vulnerable to clinically important complications from radiation toxicity. The following table outlines radiation doses that are generally considered tolerance thresholds for these normal structures in the CNS.

<table>
<thead>
<tr>
<th>Radiation tolerance doses for normal tissues</th>
<th>TD 5/5 (Gy) a</th>
<th>TD 50/5 (Gy) b</th>
<th>Complication End Point</th>
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<tbody>
<tr>
<td>Portion of organ involved</td>
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<tr>
<td>Portion of organ involved</td>
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</tbody>
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Intensity-Modulated Radiotherapy (IMRT): Central Nervous System Tumors 8.01.59

<table>
<thead>
<tr>
<th>1/3</th>
<th>2/3</th>
<th>3/3</th>
<th>1/3</th>
<th>2/3</th>
<th>3/3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain stem</td>
<td>60</td>
<td>53</td>
<td>50</td>
<td>NP</td>
<td>NP</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>50 (5-10 cm)</td>
<td>NP</td>
<td>47 (20 cm)</td>
<td>70 (5-10 cm)</td>
<td>NP</td>
</tr>
<tr>
<td>Optic nerve and chiasm</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>Retina</td>
<td>45</td>
<td>45</td>
<td>45</td>
<td>65</td>
<td>65</td>
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<tr>
<td>Eye lens</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>18</td>
<td>18</td>
</tr>
</tbody>
</table>

Necrosis, infarct
Myelitis, necrosis
Blindness
Cataract requiring intervention

Radiation tolerance doses for the cochlea have been reported to be 50 Gy
aTD 5/5, the average dose that results in a 5% complication risk within 5 years
bTD 50/5, the average dose that results in a 50% complication risk within 5 years
NP: not provided
cm=centimeters

The tolerance doses in the table are a compilation from the following two sources:

- Kehwar TS, Sharma SC. Use of normal tissue tolerance doses into linear quadratic equation to estimate normal tissue complication probability. http://www.rooj.com/Radiation%20Tissue%20Tolerance.htm

### Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
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<tbody>
<tr>
<td>Individuals: With malignant brain tumors</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td></td>
<td>- Intensity-modulated radiotherapy</td>
<td>- 3-dimensional conformal radiotherapy</td>
<td>- Overall survival</td>
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<td>- Disease-specific survival</td>
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<td>- Treatment-related morbidity</td>
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<td></td>
<td>- Treatment-related morbidity</td>
</tr>
<tr>
<td>Individuals: With brain metastases</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td></td>
<td>- Intensity-modulated radiotherapy to avoid hippocampal exposure</td>
<td>- Whole-brain radiotherapy</td>
<td>- Overall survival</td>
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<td></td>
<td></td>
<td></td>
<td>- Disease-specific survival</td>
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<td>- Treatment-related morbidity</td>
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Radiotherapy is an integral component in the treatment of many brain tumors, both benign and malignant. Intensity-modulated radiotherapy (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 specific anatomic areas at the same time as delivering radiation to a larger target volume.
For individuals who have malignant brain tumors who receive IMRT, the evidence includes dose-planning studies, nonrandomized comparison studies, and case series. Relevant outcomes are overall survival, disease-specific survival, morbid events, functional outcomes, and treatment related morbidity. Dose-planning studies have shown that IMRT delivers adequate radiation doses to tumors at the same time as reducing radiation exposure to sensitive brain areas. Case series results are consistent with low radiation toxicity, but have not demonstrated better tumor control or improved survival with IMRT. The evidence is sufficient to determine qualitatively that the technology results in a meaningful 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, morbid events, functional outcomes, and treatment related morbidity. 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. Case series results are consistent with low radiation toxicity, but have not demonstrated better tumor control or improved survival with IMRT versus other radiotherapy techniques. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have brain tumor metastases who receive IMRT to avoid hippocampal exposure or radiation boost using IMRT, the evidence includes nonrandomized comparison studies and case series. Relevant outcomes are overall survival, disease-specific survival, morbid events, functional outcomes, and treatment related morbidity. One prospective nonrandomized comparison study using IMRT to avoid hippocampal exposure showed less cognitive decline with this technique compared to a prespecified historical control. Limitations of the historical control design and other aspects of the study made the study less conclusive. The role of hippocampal radiation exposure as a cause of cognitive decline is less certain and thus more definitive studies are needed. Studies of radiation boosts delivered using IMRT are case series, which not permit conclusions that IMRT results in improved patient outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Due to the limitations in this evidence, this evidence review underwent clinical vetting in 2012. There was near-uniform consensus that use of IMRT in the central nervous system (CNS) is at least as effective as 3-dimensional conformal radiotherapy and that, given the possible adverse events that could result if nearby critical structures receive toxic radiation doses, IMRT dosimetric improvements should be accepted as meaningful evidence for its benefit. The results of the vetting, together with a strong indirect chain of evidence and the potential to reduce harms, led to the decision that IMRT may be considered medically necessary for the treatment of tumors of the CNS that are in close proximity to organs at risk.
**Background**

RT and brain tumors

The standard approach to the treatment of brain tumors depends on the type and location of tumor. For glioblastoma multiforme (GBM), a malignant high-grade tumor, treatment is multimodal, with surgical resection followed by adjuvant radiation therapy and chemotherapy. (1)

For benign and low-grade brain tumors, gross total resection remains the primary goal. However, RT may be used in selected cases. Some examples are when total resection is not possible, when a more conservative surgical approach may be necessary to achieve long-term treatment goals, and with atypical tumors that may need radiotherapy 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. (2)

Brain metastases occur in up to 40% of adults with cancer and can shorten survival and detract from quality of life. Many patients who develop brain metastases will eventually 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. (3) Stereotactic radiosurgery (SRS) may be able to replace surgery in certain circumstances, delivering obliteratively high single doses to discrete metastases. (3) For bulky cerebral metastases, level one 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 II” or SRS) and its additional labor and expense. (3) Another indication for 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.

**Radiation techniques**

Conventional external-beam radiation therapy. Over the past several decades, methods to plan and deliver radiotherapy have evolved in ways that permit more precise targeting of tumors with complex geometries. Most early trials used 2-dimensional treatment planning based on flat images and radiation beams with cross-sections of uniform intensity that were sequentially aimed at the tumor along 2 or 3 intersecting axes. Collectively, these methods are termed “conventional external-beam radiotherapy.”

3-dimensional conformal radiotherapy (3D-CRT). Treatment planning evolved by using 3-dimensional images, usually from computed tomography (CT) scans, to delineate the boundaries of the tumor and discriminate tumor tissue from adjacent normal tissue and nearby organs at risk for radiation damage. Computer
algorithms were developed to estimate cumulative radiation dose delivered to each
volume of interest by summing the contribution from each shaped beam. Methods
also were developed to position the patient and the radiation portal reproducibly
for each fraction and immobilize the patient, thus maintaining consistent beam
axes across treatment sessions. Collectively, these methods are termed 3-
dimensional conformal radiation therapy (3D-CRT).

**Intensity-modulated radiotherapy (IMRT).** IMRT, which uses computer software
and CT and magnetic resonance imaging (MRI) images, offers better conformity
than 3D-CRT, as it is able to modulate the intensity of the overlapping radiation
beams projected on the target and to use multiple shaped treatment fields. It uses
a device (a multileaf collimator, MLC) which, coupled to a computer algorithm,
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 conformity may permit escalated tumor doses without increasing
normal tissue toxicity and thus may 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
toxicities by avoiding overdosing.

Technologic development has produced advanced techniques that may further
improve RT treatment by improving dose distribution. These techniques are
considered variations of IMRT. Volumetric modulated arc therapy (VMAT) delivers
radiation from a continuous rotation of the radiation source. The principal
advantage of VMAT 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.

IMRT methods to plan and deliver RT are not uniform. IMRT may use beams that
remain on as MLCs move around the patient (dynamic MLC) or that are off during
movement and turn on once the MLC reaches prespecified positions (“step and
shoot” technique). A third alternative uses a very narrow single beam that moves
spirally around the patient (tomotherapy). Each method uses different computer
algorithms to plan treatment and yields somewhat different dose distributions in
and outside the target. Patient position can alter target shape and thus affect
treatment plans. Treatment plans are usually based on 1 imaging scan, a static
3D-CT image. Current methods seek to reduce positional uncertainty for tumors
and adjacent normal tissues by various techniques. Patient immobilization cradles
and skin or bony markers are used to minimize day-to-day variability in patient
positioning. In addition, many tumors have irregular edges that preclude drawing tight margins on CT scan slices when radiation oncologists contour the tumor volume. It is unknown whether omitting some tumor cells or including some normal cells in the resulting target affects outcomes of IMRT.

**Regulatory status**
The U.S. Food and Drug Administration (FDA) has approved a number of devices for use in intensity-modulated radiotherapy (IMRT), including several linear accelerators and multileaf collimators. Examples of approved devices and systems are the NOMOS Slit Collimator (BEAK™) (NOMOS Corp.), the Peacock™ System (NOMOS Corp.), the Varian Multileaf Collimator with dynamic arc therapy feature (Varian Oncology Systems), the Saturne Multileaf Collimator (GE Medical Systems), the Mitsubishi 120 Leaf Multileaf Collimator (Mitsubishi Electronics America Inc.), the Stryker Leibinger Motorized Micro Multileaf Collimator (Stryker Leibinger), the Mini Multileaf Collimator, model KMI (MRC Systems GMBH), and the Preference® IMRT Treatment Planning Module (Northwest Medical Physics Equipment Inc.).

**Rationale**

**Literature Review**
This evidence review was created in April 2012 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through June 2, 2017.

Multiple-dose planning studies generate 3-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (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 IMRT spreads 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 vs alternative radiation delivery would constitute definitive evidence of 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.

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 overall survival (OS) due to factors discussed above. Thus, outcomes of interest are toxicity, quality of life, locoregional recurrence, and OS.

The literature on the use of IMRT in the central nervous system consists of dosimetry planning studies, nonrandomized comparison studies, and case series. Comparative studies using IMRT vs other conformal radiation modalities (eg, 3D-CRT) were selected if found.

**Malignant Brain Tumors**

**Systematic Reviews**

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

For the 6 articles related to planning studies that compared 3D-CRT with IMRT, one (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); the remaining studies suggested that IMRT and 3D-CRT provided similar PTV coverage, with differences between 0% and 1%. Target dose conformity was 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, three were retrospective; one was a prospective phase 1 study; and four were prospective phase 2 single-institution studies. Of these eight, two used conventional total dose and dose per fraction, two 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 effects 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 study recording grade 4 adverse effects with an incidence of 20%. One- and 2-year OS 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 (PFS) rates ranged from 0% to 71.4% at 1 year from 0% to 53.6% at 2 years. The median PFS ranged from 2.5 to 12 months.

Reviewers also carried out a comprehensive qualitative comparison using data reported in the literature on similar non-IMRT clinical studies and offered the following conclusions. 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 from case to case. IMRT was 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.

This evidence 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 the administration of chemotherapy varied across studies.

**Dose-Planning Studies**

A representative sample of dose-planning, case series, and comparative studies are discussed next. For example, MacDonald et al (2007) compared the dosimetry of IMRT with 3D-CRT in 20 patients treated for high-grade glioma. Prescription dose and normal tissue constraints were identical for the 3D-CRT and IMRT treatment plans. The IMRT plan yielded superior target coverage 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% \((p=0.004)\) and the percent volume of brain receiving a dose greater than 18 Gy, 24 Gy, and 45 Gy by 10\% \((p=0.059)\), 14\% \((p=0.015)\), and 40\% \((p<0.001)\), respectively. With IMRT, the percent volume of optic chiasm receiving more than 45 Gy was reduced by 30.4\% \((p=0.047)\). Compared with 3D-CRT, IMRT significantly increased the tumor control probability \((p<0.001)\) and lowered the normal-tissue complication probability for brain and brainstem \((p<0.033)\).

Narayana et al (2006) compared IMRT treatment plans with 3D plans performed in 20 patients of a case series of 58 patients. Regardless of tumor location, IMRT did not improve 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**

Huang et al (2002) compared ototoxicity with conventional (2-dimensional) radiotherapy (RT; \(n=11\)) and IMRT \((n=15)\) in 26 pediatric patients with medulloblastoma. All patients also received chemotherapy. Compared with conventional RT, IMRT delivered 68\% of the radiation dose to the auditory apparatus, with full doses to the PTV. The median follow-up for audiometric evaluation was 51 months (range, 9-107 months) for the conventional RT group and 18 months (range, 8-37 months) for the group that received IMRT. At follow-
up, 13% of the IMRT group had grade 3 or 4 hearing loss compared with 64% of the conventional RT group (p<0.014).

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). In 161 patients, treatment margins were not associated with treatment failure. There was no difference in treatment failure rates between IMRT and 3D-CRT.

**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. Limited comparative evidence has shown lower rates of hearing loss with IMRT than with conventional RT. 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**
A representative sample of case series evaluating clinical outcomes in patients with benign tumors undergoing IMRT is discussed next. 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 the results of the treatment of complex-shaped meningiomas at the skull base with IMRT. 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. Overall local tumor control 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 outcomes of treating pituitary adenomas with IMRT. 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 PFS of 97%. One patient who received more than 46 Gy experienced optic neuropathy 8 months after radiation.

Sajja et al (2005) reported on outcomes for 35 patients with 37 meningiomas treated with IMRT. Tumor histology was benign in 35 tumors 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 been previously treated with
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.

Uy et al (2002) assessed the safety and efficacy of IMRT for intracranial meningioma in 40 patients treated between 1994 and 1999. Twenty-five patients received IMRT after surgery either as adjuvant therapy for incomplete resection or for recurrence, and 15 patients received definitive IMRT after a presumptive diagnosis of meningioma based on imaging. Thirty-two patients had skull-base lesions, and 8 had non-skull-base lesions. Follow-up ranged from 6 to 71 months (median, 30 months). Defined normal structures generally received a significantly lower radiation dose than the target. The most common acute central nervous system toxicity was a mild headache, usually relieved with steroids. One patient experienced Radiation Therapy Oncology Group grade 3 acute central nervous system toxicity, and two experienced grade 3 or higher late central nervous system toxicity, with one possible treatment-related death. No toxicity was observed with mean doses to the optic nerve or chiasm up to 47 Gy and maximum doses up to 55 Gy. Cumulative 5-year local control, PFS, and OS were 93%, 88%, and 89%, respectively.

Section Summary: Benign Brain Tumors
The evidence on IMRT for the treatment of benign brain tumors includes case series. Case series results are consistent with 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
IMRT 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, the latter having been shown to be more effective than WBRT alone in an RCT.

Nonrandomized Comparative Studies
In 2014, Gondi et al published a study evaluating IMRT as a method to avoid radiation exposure to the hippocampus and prevent adverse cognitive events in patients receiving WBRT. Dosimetry studies had previously established techniques that avoided radiation exposure to this region but still provided coverage and conformity to the remaining brain. Dosimetry studies alone have not been sufficient to establish IMRT as a standard treatment because the toxic effects of radiation to the hippocampus are less well established. The Gondi 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<0.001). 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 study did not provide conclusive evidence that hippocampal-sparing IMRT causes less cognitive decline.

Case Series
A retrospective study published in 2014 was designed to evaluate the feasibility of WBRT plus simultaneous integrated boost with IMRT for inoperable brain metastases of non-small-cell lung cancer (NSCLC). Twenty-nine NSCLC patients with 87 inoperable brain metastases were included. All patients received WBRT at a dose of 40 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 the 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 was greater than 5, when they had fewer than 3 intracranial lesions, and when they had a 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 epidermal growth factor receptor tyrosine kinase inhibitor 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 stereotactic radiosurgery. For both indications, studies are not definitive regarding improvements in health outcomes.
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 case series. Relevant outcomes are overall survival, disease-specific survival, morbid events, functional outcomes, and treatment-related morbidity. Case series results are consistent with 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 a meaningful 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 are consistent with low radiation toxicity but have not demonstrated better tumor control or improved survival with IMRT vs other radiotherapy 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. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have brain tumor metastases who receive IMRT to avoid hippocampal exposure, the evidence includes nonrandomized comparison studies and case series. Relevant outcomes are overall survival, disease-specific survival, functional outcomes, and treatment-related morbidity. One prospective nonrandomized comparison study using IMRT to avoid hippocampal exposure showed less cognitive decline with IMRT than with a prespecified historical control. Limitations of the historical control design and other aspects of the study make conclusions uncertain. The role of hippocampal radiation exposure as a cause of cognitive decline is less certain; thus, more definitive studies are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Clinical Input From 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.

While this policy was under review in 2012, input was received from 3 specialty medical societies (8 reviewers) and 3 academic medical centers (3 reviewers). There was 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 that sufficient evidence exists for IMRT to be 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**
The National Comprehensive Cancer Network guidelines on central nervous system cancers (v.1.2016) state that: “When RT [radiotherapy] is given to patients with low-grade gliomas, it is administered with restricted margins.... Every attempt should be made to decrease the RT dose outside the target volume. This can be achieved with 3-dimensional planning or intensity-modulated RT.”

The guidelines do not address the use of intensity-modulated radiotherapy in high-grade tumors or metastases of the central nervous system.

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

**Medicare National Coverage**
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished or uncompleted trials that might influence this review are listed in Table 1.

**Table 1. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT03002532</td>
<td>Whole Brain Irradiation With Hippocampal Sparing for Brain Metastases From Breast Cancer: Neurocognitive Function and Prognosis Analysis</td>
<td>120</td>
<td>Aug 2017</td>
</tr>
<tr>
<td>NCT02832635</td>
<td>A Clinical Trial on Whole-brain Radiotherapy With Temozolomide Concurrent Chemotherapy or Avoidance of Hippocampus for Patients of Brain Metastases</td>
<td>256</td>
<td>Dec 2017</td>
</tr>
<tr>
<td>NCT02393131</td>
<td>Neurocognitive Outcome of Conformal Whole Brain Radiotherapy With or Without Hippocampal Avoidance for Brain Metastases: A Phase II Single Blind Randomized Trial</td>
<td>60</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT02147028</td>
<td>Hippocampal Sparing Whole Brain Radiotherapy vs Conventional Whole Brain Radiotherapy in Patients With Brain Metastases (HIPPO)</td>
<td>84</td>
<td>Dec 2019</td>
</tr>
<tr>
<td>NCT02360215</td>
<td>Memantine Hydrochloride and Whole-Brain Radiotherapy With or Without Hippocampal</td>
<td>510</td>
<td>Nov 2020</td>
</tr>
</tbody>
</table>
Avoidance in Reducing Neurocognitive Decline in Patients With Brain Metastases

NCT02635009  Randomized Phase II/III Trial of Prophylactic Cranial Irradiation With or Without Hippocampal Avoidance for Small Cell Lung Cancer

NCT: national clinical trial.

References


Billing Coding/Physician Documentation Information

**77301** Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications

**77338** Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan

**77385** Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; simple

**77386** Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; complex

**77387** Guidance for localization of target volume for delivery of radiation treatment delivery, includes intrafraction tracking, when performed

**G6001** Ultrasonic guidance for placement of radiation therapy fields

**G6002** Stereoscopic x-ray guidance for localization of target volume for the delivery of radiation therapy

**G6015** Intensity modulated treatment delivery, single or multiple fields/arcs, via narrow spatially and temporally modulated beams, binary, dynamic MLC, per treatment session

**G6016** Compensator-based beam modulation treatment delivery of inverse planned treatment using 3 or more high resolution (milled or cast) compensator, convergent beam modulated fields, per treatment session

**ICD-10 Codes**

**C71.0-** Malignant neoplasm of brain, code range

**C71.9** Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system, code range

**C72.0-** Secondary malignant neoplasm of brain and cerebral meninges, code range

**C79.32** Range

**C79.40-** Secondary malignant neoplasm of other and unspecified parts of nervous system, code range

In 2015 Codes 0073T and 77418 were deleted.

The following CPT codes are used for simple and complex intensity-modulated radiotherapy (IMRT) delivery:

**77385**: Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; simple

**77386**: complex.

The Centers for Medicare and Medicaid Services decided not to implement these CPT codes and instead created HCPCS G codes with the language of the previous CPT codes. So the following codes may be used for IMRT:
G6015: Intensity modulated treatment delivery, single or multiple fields/arcs, via narrow spatially and temporally modulated beams, binary, dynamic MLC, per treatment session

G6016: Compensator-based beam modulation treatment delivery of inverse planned treatment using 3 or more high resolution (milled or cast) compensator, convergent beam modulated fields, per treatment session.

Code 77301 remains valid:

77301: Intensity-modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications.

The following CPT code may also be used:

77338: Multi-leaf collimator (MLC) device(s) for intensity-modulated radiation therapy (IMRT), design and construction per IMRT plan.

Code 77338 is to be reported only once per IMRT plan.

**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/1/13</td>
<td>New policy; may be considered medically necessary.</td>
</tr>
<tr>
<td>6/1/14</td>
<td>Policy Statement added that IMRT is considered not medically necessary for the treatment of tumors of the central nervous system for indications not meeting the criteria for medically necessary.</td>
</tr>
<tr>
<td>1/1/2015</td>
<td>New HCPCS codes. No policy statement changes.</td>
</tr>
<tr>
<td>6/1/15</td>
<td>Title changed from “radiation therapy” to “radiotherapy” to be consistent with other MPRM policies. Policy statements unchanged.</td>
</tr>
<tr>
<td>6/1/16</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>10/1/16</td>
<td>For other indications, policy statement changed to investigational.</td>
</tr>
<tr>
<td>6/1/17</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>6/1/18</td>
<td>No policy statement changes.</td>
</tr>
</tbody>
</table>

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.