| 8.01.59 | Intensity-Modulated Radiotherapy: Central Nervous System Tumors | | |
|---|---|---|---|
| **Original Policy Date:** | March 30, 2015 | **Effective Date:** | August 1, 2022 |
| **Section:** | 8.0 Therapy | **Page:** | Page 1 of 23 |

## Policy Statement

I. Intensity-modulated radiotherapy may be considered **medically necessary** for individuals with malignant or benign brain tumors when dosimetric planning with standard 3-dimensional conformal radiotherapy predicts that the radiation dose to an adjacent organ (e.g.: brain stem, spinal cord, cochlea and eye structures including optic nerve and chiasm, lens and retina) would result in unacceptable normal tissue toxicity, as documented by **one or more** of the following:
   A. The target volume is in close proximity to critical structures that must be protected and **both** of the following: * (see source below)
      1. Planned 3D-CRT exposure to critical adjacent structures is above normal tissue constraints
      2. Planned IMRT exposure to these critical adjacent structures does not exceed normal tissue constraints
   B. An immediately adjacent area has been previously irradiated and abutting portals must be established with high precision
   C. Pediatric CNS tumors

II. Hippocampal-avoiding intensity-modulated radiotherapy may be considered **medically necessary** for individuals when **both** of the following criteria are met:
   A. With brain tumor metastases outside a 5-mm margin around either hippocampus
   B. Expected survival of 4 months or longer

III. Intensity-modulated radiotherapy is considered **investigational** for the treatment of tumors of the central nervous system for all indications not meeting the criteria above.

**NOTE**: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

## Policy Guidelines

This policy is related to cancers of the central nervous system (brain, brain stem, spinal cord and some cochlea and eye cancers with related cranial nerve involvement).

For other head and neck cancers, those arising from the oral cavity and lip, larynx, hypopharynx, oropharynx, nasopharynx, paranasal sinuses and nasal cavity, salivary glands, thyroid and occult primaries in the head and neck region see Blue Shield of California Medical Policy: Intensity-Modulated Radiotherapy: Cancer of the Head and Neck or Thyroid

Organs at risk are defined as normal tissues whose radiation sensitivity may significantly influence treatment planning and/or prescribed radiation dose. Organs at risk may be particularly vulnerable to clinically important complications from radiation toxicity. Table PG1 outlines radiation doses generally considered tolerance thresholds for these normal structures in the central nervous system. Dosimetry plans may be reviewed to demonstrate that radiation by 3-dimensional conformal radiotherapy would exceed tolerance doses to structures at risk.

*The following Normal Tissue Constraint Guidelines are derived from the textbook: Radiation Oncology: A Question-Based Review published by Lippincott Williams & Wilkins, 2010 [author: Hristov et al., 2010]). According to the author, most dosages were derived from randomized studies or consensus guidelines however; pediatric dose constraints will vary greatly from protocol to protocol. Sources used in the development of the guidelines included the American Brachytherapy Society (ABS); Clinical practice guidelines from Johns Hopkins Hospital (JHH); the

International Journal of Radiation Oncology *Biology* Physics (IJROBP); the National Comprehensive Cancer Network (NCCN), Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC); and the Radiation Therapy Oncology Group (RTOG) protocols at the time of publication.

The following guidelines are only intended to serve as a guide and may not be applicable to all clinical scenarios.

| Organ | Constraints |
|---|---|
| **Central Nervous System (1.8-2.0 Gray/fraction [Gy/fx])** | |
| • Spinal Cord | max 50 Gy (full cord cross-section); tolerance increases by 25% 6 mos after 1st course (for re-irradiation) |
| • Brain | max 72 Gy (partial brain); avoid >2 Gy/fx or hyperfractionation |
| • Chiasm/Optic Nerves | max 55 Gy |
| • Brainstem | Entire brainstem <54 Gy, V59 Gy <1–10 cc |
| • Eyes (globe) | mean <35 Gy, max 54 Gy |
| • Lens | max 7 Gy |
| • Retina | max 50 Gy |
| • Lacrimal Gland | max 40 Gy |
| • Inner ear/cochlea | mean </=45 Gy (consider constraining to </=35 Gy with concurrent cisplatin) |
| • Pituitary gland | max 45 Gy (for panhypopituitarism, lower for GH deficiency) |
| • Cauda equina | max 60 Gy |
| **Central Nervous System (single fraction)** | |
| • Spinal Cord | max 13 Gy (if 3 fxs, max 20 Gy) |
| • Brain | V12 Gy <5–10 cc |
| • Chiasm/Optic Nerves | max 10 Gy |
| • Brainstem | max 12.5 Gy |
| • Sacral plexus | V18 <0.035 cc, V14.4 <5 cc |
| • Cauda equina | V16 <0.035 cc, V14 <5 cc |
| **Head and Neck (1.8–2.0 Gy/fx)** | |
| • Parotid gland(s) | mean <25 Gy (both glands) or mean <20 Gy (1 gland) |
| • Submandibular gland(s) | mean <35 Gy |
| • Larynx | mean </=44 Gy, V50 </=27%, max 63–66 Gy (when risk of tumor involvement is limited) |
| • TMJ/mandible | max 70 Gy (if not possible, then V75 <1 cc) |
| • Oral cavity | Non-oral cavity cancer: mean <30 Gy, avoid hot spots >60 Gy Oral cavity cancer: mean <50 Gy, V55 <1 cc, max 65 Gy |
| • Esophagus (cervical) | V45 <33% |
| • Pharyngeal constrictors | mean <50 Gy |
| • Thyroid | V26 <20% |
| **Thoracic (1.8–2.0 Gy/fx)** | |
| • Brachial plexus | max 66 Gy, V60 <5% |
| • Lung (combined lung for lung cancer treatment) | mean <20–23 Gy, V20 <30%–35% |
| • Lung (ipsilateral lung for breast cancer treatment) | V25 <10% |
| • Single lung (after pneumonectomy) | V5 <60%, V20 <4–10%, MLD <8 Gy |
| • Bronchial tree | max 80 Gy |
| • Heart (lung cancer treatment) | Heart V45 <67%; V60 <33% |
| • Heart (breast cancer treatment) | V25 <10% |
| • Esophagus | V50 <32% ;V60 <33% |
| **Thoracic (hypofractionation)** | |
| **Note: the max dose limits refer to volumes >0.035 cc (~3 mm³).** | |

| Organ | Constraints |
|---|---|
| • Spinal cord | 1 fraction: 14 Gy<br>3 fractions: 18 Gy (6 Gy/fx)<br>4 fractions: 26 Gy (6.5 Gy/fx)<br>5 fractions: 30 Gy (6 Gy/fx) |
| • Esophagus | 1 fraction: 15.4 Gy<br>3 fractions: 30 Gy (10 Gy/fx)<br>4 fractions: 30 Gy (7.5 Gy/fx)<br>5 fractions: 32.5 Gy (6.5 Gy/fx) |
| • Brachial plexus | 1 fraction: 17.5 Gy<br>3 fractions: 21 Gy (7 Gy/fx)<br>4 fractions: 27.2 Gy (6.8 Gy/fx)<br>5 fractions: 30 Gy (6 Gy/fx) |
| • Heart/Pericardium | 1 fraction: 22 Gy<br>3 fractions: 30 Gy (10 Gy/fx)<br>4 fractions: 34 Gy (8.5 Gy/fx)<br>5 fractions: 35 Gy (7 Gy/fx) |
| • Great vessels | 1 fraction: 37 Gy<br>3 fractions: 39 Gy (13 Gy/fx)<br>4 fractions: 49 Gy (12.25 Gy/fx)<br>5 fractions: 55 Gy (11 Gy/fx) |
| • Trachea/Large Bronchus | 1 fraction: 20.2 Gy<br>3 fractions: 30 Gy (10 Gy/fx)<br>4 fractions: 34.8 Gy (8.7 Gy/fx)<br>5 fractions: 40 Gy (8 Gy/fx) |
| • Rib | 1 fraction: 30 Gy<br>3 fractions: 30 Gy (10 Gy/fx)<br>4 fractions: 32 Gy (7.8 Gy/fx)<br>5 fractions: 32.5 Gy (6.5 Gy/fx) |
| • Skin | 1 fraction: 26 Gy<br>3 fractions: 30 Gy (10 Gy/fx)<br>4 fractions: 36 Gy (9 Gy/fx)<br>5 fractions: 40 Gy (8 Gy/fx) |
| • Stomach | 1 fraction: 12.4 Gy<br>3 fractions: 27 Gy (9 Gy/fx)<br>4 fractions: 30 Gy (7.5 Gy/fx)<br>5 fractions: 35 Gy (7 Gy/fx) |
| **Gastrointestinal (GI) (1.8–2.0 Gy/fx)** | |
| • Stomach | TD 5/5 whole stomach: 45 Gy |
| • Small bowel | V45 <195 cc |
| • Liver (metastatic disease) | mean liver <32 Gy (liver = normal liver minus gross disease) |
| • Liver (primary liver cancer) | mean liver <28 Gy (liver = normal liver minus gross disease) |
| • Colon | 45 Gy, max dose 55 Gy |
| • Kidney (bilateral) | mean <18 Gy, V28 <20%, V23 Gy <30%, V20 <32%, V12 <55%. If mean kidney dose to 1 kidney >18 Gy, then constrain remaining kidney to V6 <30%. |
| **Gastrointestinal (GI) (single fraction)** | |
| • Duodenum | V16 <0.035 cc, V11.2 <5 cc |
| • Kidney (Cortex) | V8.4 <200 cc |
| • Kidney (Hilum) | V10.6 <66% |
| • Colon | V14.3 <20 cc, V18.4 <0.035 cc |
| • Jejunum/Ileum | V15.4 <0.035 cc, V11.9 <5 cc |
| • Stomach | V16 <0.035 cc, V11.2 <10 cc |
| • Rectum | V18.4 <0.035 cc, V14.3 <20 cc |
| **Genitourinary (GU) (1.8-2.0 Gy/fx)** | |
| • Femoral heads | V50 <5% |
| • Rectum | V75 <15% , V70 <20%, V65 <25%,<br>V60 <35%, V50 <50% |
| • Bladder | V80 <15%, V75 <25%, V70 <35%, |

| Organ | Constraints |
|---|---|
| | V65 <50% |
| • Testis | V3 <50% |
| • Penile bulb | Mean dose to 95% of the volume <50 Gy. D70 </=70 Gy, D50 </=50 Gy |
| Genitourinary (GU) (LDR prostate brachytherapy) | |
| • Urethra | Volume of urethra receiving 150% of prescribed dose (Ur150) <30% |
| • Rectum | Volume of rectum receiving 100% of prescribed dose (RV100) <0.5 cc |
| **Gynecological (GYN)** | |
| • Bladder point (cervical brachytherapy) | Max 80 Gy (LDR equivalent dose) |
| • Rectal point (cervical brachytherapy) | Max 75 Gy (LDR equivalent dose) |
| • Proximal vagina (mucosa) (cervical brachytherapy) | Max 120 Gy (LDR equivalent dose) |
| • Distal vagina (mucosa) (cervical brachytherapy) | Max 98 Gy (LDR equivalent dose |

## Coding

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

The Centers for Medicare & Medicaid Services did not implement these CPT codes and instead created HCPCS G codes with the language of the previous CPT codes. Therefore, 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.

The following codes may also be used:

- **77261**: Therapeutic radiology treatment planning; simple
- **77262**: Therapeutic radiology treatment planning; intermediate
- **77263**: Therapeutic radiology treatment planning; complex
- **77293**: Respiratory motion management simulation (List separately in addition to code for primary procedure)
- **77300**: Basic radiation dosimetry calculation, central axis depth dose calculation, TDF, NSD, gap calculation, off axis factor, tissue inhomogeneity factors, calculation of non-ionizing radiation surface and depth dose, as required during course of treatment, only when prescribed by the treating physician

- **77306**: Teletherapy isodose plan; simple (1 or 2 unmodified ports directed to a single area of interest), includes basic dosimetry calculation(s)
- **77307**: Teletherapy isodose plan; complex (multiple treatment areas, tangential ports, the use of wedges, blocking, rotational beam, or special beam considerations), includes basic dosimetry calculation(s)
- **77331**: Special dosimetry (e.g., TLD, microdosimetry) (specify), only when prescribed by the treating physician
- **77332**: Treatment devices, design and construction; simple (simple block, simple bolus)
- **77334**: Treatment devices, design and construction; complex (irregular blocks, special shields, compensators, wedges, molds or casts)
- **77370**: Special medical radiation physics consultation
- **77470**: Special treatment procedure (e.g., total body irradiation, hemibody radiation, per oral or endocavitary irradiation)
- **77336**: Continuing medical physics consultation, including assessment of treatment parameters, quality assurance of dose delivery, and review of patient treatment documentation in support of the radiation oncologist, reported per week of therapy
- **77427**: Radiation treatment management, 5 treatments
- **77014**: Computed tomography guidance for placement of radiation therapy fields
- **77417**: Therapeutic radiology port image(s)
- **77387**: Guidance for localization of target volume for delivery of radiation treatment, 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
- **G6017**: Intra-fraction localization and tracking of target or patient motion during delivery of radiation therapy (e.g., 3D positional tracking, gating, 3D surface tracking), each fraction of treatment

**Allowable Codes and Frequencies for IMRT/Proton**

| Description | Code | Maximum per course of treatment | Notes |
|---|---|---|---|
| Clinical Treatment Planning | 77261, 77262 or 77263 | 1 | |
| Simulation | 77280, 77285, 77290 | 0 | May not be billed with 77301. 1 unit of 77290 + 1 boost is allowed for proton therapy when using 77295 instead |
| Verification Simulation | 77280 | 0 | One per simulation allowed |
| Respiratory Motion Management | 77293 | 0 | 1 for breast, lung, and upper abdominal or thoracic cancer areas |
| 3D CRT Plan | 77295 | 0 | May not be billed with 77301. 1 unit may be allowed for proton therapy. |
| IMRT Plan | 77301 | 1 | If comparison 3D plan is generated, it is included in 77301 |
| Basic Dosimetry | 77300 | 4+ 1 boost, up to a max of 10 with documentation | 0 if billed with 77306, 77307, 77321, 0394T or 0395T |
| Teletherapy Isodose Plan, Simple | 77306 | 1 for mid-Tx change in volume/contour | Not on the same day as 77300; may not bill 77306 and 77307 together; documentation of medical necessity is required for more than 1 |
| Teletherapy Isodose Plan, Complex | 77307 | 1 for mid-Tx change in volume/contour | Not on the same day as 77300; may not bill 77306 and 77307 together; documentation of medical necessity is required for more than 1 |
| Special Dosimetry Calculation | 77331 | 0 | Needs documentation for review |

| Description | Code | Maximum per course of treatment | Notes |
|---|---|---|---|
| Treatment Devices, Designs, and Construction | 77332, 77333, 77334 | 1, 5 or 10 | -If billed w/ MLC (77338): 1<br>-If billed w/o MLC: 5 (any combination)<br>-More may be allowed when documentation of medical necessity is provided (such as additional beams), maximum of 10 |
| Multi-leaf Collimater (MLC) | 77338 | 1 | MLC may not be reported in conjunction with HCPCS G6016 |
| Special Radiation Physics Consult | 77370 | 0 | May allow x 1; documentation of medical necessity required |
| Special MD Consultation (Special Tx Procedure) | 77470 | 0 | May allow x 1; documentation of medical necessity required |
| Medical Physics Management | 77336 | 8 | Allowed once per 5 courses of therapy |
| Radiation Treatment Management | 77427 | 8 | Allowed once per 5 courses of therapy |
| Radiation (IMRT or Proton) Delivery, prostate and breast cancer | IMRT 77385 or G6015;<br><br>Proton 77520, 77522, 77523 | Using IMRT or Proton:<br>28 for prostate cancer<br><br>Using IMRT only:<br>-16 for breast cancer without boost<br>-24 for breast cancer with boost (IMRT only) | Prostate cancer: Documentation of medical necessity needed for more than 28 treatments<br><br>Breast cancer: documentation of medical necessity needed for treatments beyond 16 IMRT delivery sessions without boost and/or 24 IMRT delivery sessions with boost. |
| Radiation (IMRT or Proton) Delivery, all other cancers | IMRT 77385, 77386; or G6015-G6016:<br><br>Proton 77520, 77522, 77523, 77525 | No limit | All cancers other than hypofractionated prostate or breast |

## Description

Radiotherapy (RT) is an integral component of treating 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. Intensity-modulated radiotherapy also allows additional radiation to penetrate specific anatomic areas simultaneously, delivering radiation at a larger target volume.

## Related Policies

- Hematopoietic Cell Transplantation for Central Nervous System Embryonal Tumors and Ependymoma
- Intensity-Modulated Radiotherapy: Cancer of the Head and Neck or Thyroid
- Intracavitary Balloon Catheter Brain Brachytherapy for Malignant Gliomas or Metastasis to the Brain
- Intraoperative Radiotherapy
- Radiation Oncology
- Stereotactic Radiosurgery and Stereotactic Body Radiotherapy

## Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

## 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 the 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 the FDA through the 510(k) process is the Varian IMRT system (Varian Medical Systems). FDA product code: IYE.

## Rationale

### Background

#### Radiotherapy Techniques

Radiation therapy may be administered externally (i.e., a beam of radiation is directed into the body) or internally (i.e., 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 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**

Intensity-modulated radiotherapy 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, surrounding tissues, and organs at risk, computer software optimizes the location, shape, and intensities of the beam 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.

**Literature Review**

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are the 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 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 technology, 2 domains are examined: the relevance, and 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. Randomized controlled trials 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 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 events from IMRT versus 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 event 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 patients who have malignant brain tumors is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does treatment with IMRT improve health outcomes in individuals with malignant brain tumors?

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. Intensity-modulated radiotherapy is a method that allows adequate radiation to the tumor while minimizing the dose to surrounding normal tissues and critical structures. Intensity-modulated radiotherapy also allows additional radiation to penetrate specific anatomic areas simultaneously, delivering radiation at a larger target volume.

***Comparators***
The following practice 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 the 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 long-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 of the clinical and technical issues of using IMRT in newly diagnosed glioblastoma multiforme.[2] 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 RCTs 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<.001)[3]; 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, 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 (PFS) rates ranged from 0% to 71.4% at 1 year and from 0% to 53.6% at 2 years. The median PFS 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. Intensity-modulated radiotherapy was somewhat better than 3D-CRT in reducing the maximum dose delivered to the organs at risk, although the extent varied by case. Intensity-modulated radiotherapy 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 with 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 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 brainstem (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 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 the 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 (odds ratio [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 patients 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 question addressed in this evidence review is: Does treatment with IMRT improve health outcomes in individuals with benign brain tumors?

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. Intensity-modulated radiotherapy is a method that allows adequate radiation to the tumor while minimizing the dose to surrounding normal tissues and critical structures. Intensity-modulated radiotherapy also allows additional radiation to penetrate specific anatomic areas simultaneously, delivering radiation at a larger target volume.

***Comparators***
The following practice 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 the 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 long-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**
**Case Series**
The evidence for the 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 the World Health Organization (WHO), 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 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 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.[11] 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 to 62.4 months). Fifty-four percent of the meningiomas had received surgery or radiosurgery before IMRT, and 46% were treated with IMRT, primarily after 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 OS at a mean followup 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 versus 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 patients 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 solitary brain metastasis, randomized studies have shown that surgical excision followed by 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 a 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 question addressed in this evidence review is: Does treatment with IMRT improve health outcomes in individuals with brain metastases when it is necessary to avoid hippocampal exposure?

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 practice 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 the 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 long-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**
**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 hazard ratio [HR] 0.74, 95% CI 0.58 to 0.95) without any difference between groups in OS (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).

**Table 1. Summary of RCT 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<br><br>HA-WBRT: Bilateral hippocampal contours were manually generated on a fused thin-slice MRI-CT image set and expanded by 5 mm to generate the HA region + 30 Gy in 10 fractions) + memantine (5 to 7mg/day titrated to 20 to 28 mg/day) | N=257<br><br>WBRT (30 Gy in 10 fractions) + memantine (5 to 7 mg/day titrated to 20 to 28 mg/day) |

HA-WBRT: hippocampal-avoiding whole body radiation; MRI-CT: magnetic resonance imaging-computed tomography; RCT: randomized controlled trial.

**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/RR (95% CI) | unadjusted HR 0.76 (95% CI 0.60 to 0.98)[1]<br>adjusted HR 0.74 (95% CI 0.58 to 0.95)<br>ARD -0.10 (95% CI -0.19 to -0.02) | HR, 1.13 (95% CI 0.90 to 1.41) | 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 | Blinding | Selective Reporting | Data Completeness | Power | Statistical |
|---|---|---|---|---|---|---|
| Brown et al (2020); NRG Oncology CC001 (Phase 3)[13] | -- | 1. Due to the nature of the treatment, blinding was deemed not possible. | -- | 1. The proportion of patients withdrawing from the study in the first 6 | -- | 3. Risk estimates were not reported for individual timepoints for the primary |

| Study | Allocation | Blinding | Selective Reporting | Data Completeness | Power | Statistical |
|---|---|---|---|---|---|---|
| | | However, assessors were blinded for the cognitive outcome. | | months ranged from 14% to 27%; the study protocol adjusted for missing data using imputation | | 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 and prevent adverse cognitive events 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 endpoint 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 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 non-small-cell lung cancer patients with inoperable brain metastases. However, the evidence does not permit conclusions about efficacy.

**Section Summary: Brain Metastases**
For the 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 non-randomized 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 IMRT, the evidence includes dose-planning studies, nonrandomized comparison studies, and a systematic review. Relevant outcomes are OS, 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 OS, DSS, 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 RT 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 studies, and case series. Relevant outcomes are OS, DSS, functional outcomes, and treatment-related morbidity. One randomized trial and one prospective nonrandomized comparison study using IMRT to avoid hippocampal exposure showed less cognitive decline with IMRT than with either conventional 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 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.

In response to requests from Blue Cross Blue Shield Association, input was received from 3 specialty medical societies (8 reviewers) and 3 academic medical centers (3 reviewers) in 2012. There was a near-uniform consensus that intensity-modulated radiotherapy (IMRT) to treat

central nervous system tumors 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 (3D-CRT). Further, given the possible adverse events that could result if nearby critical structures receive toxic radiation doses (e.g., 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**
The National Comprehensive Cancer Network Clinical Practice Guidelines on Central Nervous System Cancers (v. 5.2020) support the use of highly conformal fractionated radiotherapy (RT) techniques (e.g., 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 (3D) 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 techniques, which include 3D-CRT and IMRT are 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 greater, the guidelines recommend considering 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 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, one 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.

**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 ongoing 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*** | | | |
| NCT02147028 | Hippocampal Sparing Whole Brain Radiotherapy vs Conventional Whole Brain Radiotherapy in Patients With Brain Metastases (HIPPO) | 23 | Feb 2021 |
| NCT04397679 | Partial Brain Radiation Therapy, Temozolomide, Chloroquine, and Tumor Treating Fields Therapy for the Treatment of Newly Diagnosed Glioblastoma | 10 | Sep 2022 |
| NCT02635009 | Randomized Phase II/III Trial of Prophylactic Cranial Irradiation With or Without Hippocampal Avoidance for Small Cell Lung Cancer | 392 | Apr 2027 |

NCT: national clinical trial.

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## Documentation for Clinical Review

**Please provide the following documentation:**

- (click here >>>) Fax Back Form for Radiation Oncology Services

## Coding

*This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.*

*The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.*

| Type | Code | Description |
|---|---|---|
| CPT® | 77014 | Computed tomography guidance for placement of radiation therapy fields |
| | 77261 | Therapeutic radiology treatment planning; simple |
| | 77262 | Therapeutic radiology treatment planning; intermediate |
| | 77263 | Therapeutic radiology treatment planning; complex |
| | 77293 | Respiratory motion management simulation (List separately in addition to code for primary procedure) |
| | 77300 | Basic radiation dosimetry calculation, central axis depth dose calculation, TDF, NSD, gap calculation, off axis factor, tissue inhomogeneity factors, calculation of non-ionizing radiation surface and depth dose, as required during course of treatment, only when prescribed by the treating physician |
| | 77301 | Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications |
| | 77306 | Teletherapy isodose plan; simple (1 or 2 unmodified ports directed to a single area of interest), includes basic dosimetry calculation(s) |
| | 77307 | Teletherapy isodose plan; complex (multiple treatment areas, tangential ports, the use of wedges, blocking, rotational beam, or |

| Type | Code | Description |
|---|---|---|
| | | special beam considerations), includes basic dosimetry calculation(s) |
| | 77331 | Special dosimetry (e.g., TLD, microdosimetry) (specify), only when prescribed by the treating physician |
| | 77332 | Treatment devices, design and construction; simple (simple block, simple bolus) |
| | 77334 | Treatment devices, design and construction; complex (irregular blocks, special shields, compensators, wedges, molds or casts) |
| | 77336 | Continuing medical physics consultation, including assessment of treatment parameters, quality assurance of dose delivery, and review of patient treatment documentation in support of the radiation oncologist, reported per week of therapy |
| | 77338 | Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan |
| | 77370 | Special medical radiation physics consultation |
| | 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, includes intrafraction tracking, when performed |
| | 77417 | Therapeutic radiology port image(s) |
| | 77427 | Radiation treatment management, 5 treatments |
| | 77470 | Special treatment procedure (e.g., total body irradiation, hemibody radiation, per oral or endocavitary irradiation) |
| **HCPCS** | 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 |
| | G6017 | Intra-fraction localization and tracking of target or patient motion during delivery of radiation therapy (e.g., 3D positional tracking, gating, 3D surface tracking), each fraction of treatment |

## Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

| Effective Date | Action |
|---|---|
| 03/30/2015 | Policy title change from Intensity Modulated Radiation Therapy (IMRT)<br>BCBSA Medical Policy adoption<br>Policy revision without position change |
| 10/01/2016 | Policy revision with position change |
| 09/01/2017 | Policy revision without position change |
| 09/01/2018 | Policy revision without position change |
| 11/01/2019 | Policy revision without position change |
| 06/01/2020 | Administrative update. Policy statement, guidelines and literature updated |

| Effective Date | Action |
|---|---|
| 11/20/2020 | Annual review. Policy statement, guidelines and literature updated. Coding update. |
| 01/01/2021 | Policy statement updated. |
| 08/01/2021 | Annual review. No change to policy statement. Policy guidelines updated. |
| 12/01/2021 | Administrative update. No change to policy statement. Policy guidelines and literature updated. |
| 08/01/2022 | Annual review. No change to policy statement. |

## Definitions of Decision Determinations

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

## Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

*Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*

## Appendix A

| POLICY STATEMENT | |
|---|---|
| **BEFORE**<br>**Red font: Verbiage removed** | **AFTER**<br>**Blue font: Verbiage Changes/Additions** |
| **Intensity-Modulated Radiotherapy: Central Nervous System Tumors 8.01.59**<br><br>**Policy Statement:**<br>Intensity-modulated radiotherapy may be considered **medically necessary** for individuals with malignant or benign brain tumors when dosimetric planning with standard 3-dimensional conformal radiotherapy predicts that the radiation dose to an adjacent organ (e.g.: brain stem, spinal cord, cochlea and eye structures including optic nerve and chiasm, lens and retina) would result in unacceptable normal tissue toxicity, as documented by **one or more** of the following:<br>I. The target volume is in close proximity to critical structures that must be protected and **both** of the following: * (see source below)<br>A. Planned 3D-CRT exposure to critical adjacent structures is above normal tissue constraints<br>B. Planned IMRT exposure to these critical adjacent structures does not exceed normal tissue constraints<br>II. An immediately adjacent area has been previously irradiated and abutting portals must be established with high precision<br><br>III. Pediatric CNS tumors<br><br>Hippocampal-avoiding intensity-modulated radiotherapy may be considered **medically necessary** for individuals when **both** of the following criteria are met:<br>I. With brain tumor metastases outside a 5-mm margin around either hippocampus<br>II. Expected survival of 4 months or longer<br><br>Intensity-modulated radiotherapy is considered **investigational** for the treatment of tumors of the central nervous system for all indications not meeting the criteria above. | **Intensity-Modulated Radiotherapy: Central Nervous System Tumors 8.01.59**<br><br>**Policy Statement:**<br>I. Intensity-modulated radiotherapy may be considered **medically necessary** for individuals with malignant or benign brain tumors when dosimetric planning with standard 3-dimensional conformal radiotherapy predicts that the radiation dose to an adjacent organ (e.g.: brain stem, spinal cord, cochlea and eye structures including optic nerve and chiasm, lens and retina) would result in unacceptable normal tissue toxicity, as documented by **one or more** of the following:<br>A. The target volume is in close proximity to critical structures that must be protected and **both** of the following: * (see source below)<br>1. Planned 3D-CRT exposure to critical adjacent structures is above normal tissue constraints<br>2. Planned IMRT exposure to these critical adjacent structures does not exceed normal tissue constraints<br>B. An immediately adjacent area has been previously irradiated and abutting portals must be established with high precision<br>C. Pediatric CNS tumors<br><br>II. Hippocampal-avoiding intensity-modulated radiotherapy may be considered **medically necessary** for individuals when **both** of the following criteria are met:<br>A. With brain tumor metastases outside a 5-mm margin around either hippocampus<br>B. Expected survival of 4 months or longer<br><br>III. Intensity-modulated radiotherapy is considered **investigational** for the treatment of tumors of the central nervous system for all indications not meeting the criteria above. |