Intracavitary Balloon Catheter Brain Brachytherapy for Malignant Gliomas or Metastasis to the Brain

Policy # 00434
Original Effective Date: 10/15/2014
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers intracavitary balloon catheter brain brachytherapy, alone or as part of a multimodality treatment regimen, for primary or recurrent malignant brain tumors to be investigational.*

Based on review of available data, the Company considers intracavitary balloon catheter brain brachytherapy also, alone or as part of a multimodality treatment regimen, for metastasis to the brain from primary solid tumors outside the brain to be investigational.*

Background/Overview
Intracavitary balloon catheter brain brachytherapy is an approach to localized radiation therapy delivered with an inflatable balloon catheter in the treatment of malignant brain lesions.

Intracavitary Balloon Catheter Brain Brachytherapy
Intracavitary balloon catheter brain brachytherapy is localized radiation therapy in the brain that requires placement of an inflatable balloon catheter in the surgical cavity, before closing the craniotomy of a resection, to remove or debulk a malignant brain mass. A radiation source is then placed in the balloon to expose surrounding brain tissue to radiation, either continuously or in a series of brief treatments. After the patient completes therapy, the radiation source is permanently removed, and the balloon catheter is surgically explanted.

Malignant Gliomas
Diffuse fibrillary astrocytoma is the most common glial brain tumor in adults. It is classified histologically into 3 grades: grade II astrocytoma, grade III anaplastic astrocytoma, and grade IV glioblastoma multiforme (GBM). Oligodendrogliomas (ODGs) are diffuse neoplasms closely related to diffuse fibrillary astrocytomas clinically and biologically. However, these tumors generally have better prognoses than diffuse astrocytomas, with mean survival times of 10 years versus 2 to 3 years. Also, ODGs apparently are more chemosensitive than astrocytomas. GBM, the most aggressive and chemoresistant astrocytoma, has survival times of less than 2 years for most patients.

Treatment of primary brain tumors begins with surgery with curative intent or optimal tumor debulking, usually followed by radiation therapy and/or chemotherapy. Survival after chemoradiotherapy largely depends on the extent of residual tumor after surgery. Therefore, tumors arising in the midline, basal ganglia, or corpus callosum or those arising in the eloquent speech or motor areas of the cortex have a
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particularly poor outcome, because they typically cannot be extensively resected. Recurrence is common after surgery for malignant gliomas, even if followed by chemoradiotherapy, because the tumors are usually diffusely infiltrating and develop resistance to chemotherapy; also, neurotoxicity limits cumulative doses of whole brain radiation. Chemotherapy regimens for gliomas usually rely on nitrosourea alkylating agents (carmustine or lomustine), temozolomide, procarbazine, vincristine, and platinum-based agents. The most common regimen combines procarbazine, lomustine (also known as CCNU), vincristine (PCV) and single or multiagent therapy with temozolomide. A biodegradable polymer wafer impregnated with carmustine (Gliadel®; Guilford Pharmaceuticals Inc.) also can be implanted into the surgical cavity as an adjunct to surgery and radiation. It is indicated for newly diagnosed high-grade malignant glioma and for recurrent GBM.

Brain Metastasis from Other Primary Malignancies
Intracranial metastases are a frequent occurrence seen at autopsy in 10% to 30% of deaths from cancer. Lung cancer is the most common source of brain metastasis (relative prevalence, 48%), followed by breast cancer (15%), unknown primary (12%), melanoma (9%), and colon cancer (5%).

Treatment goals in these patients include local control of existing metastases, regional control to prevent growth of undetected metastases, extending the duration of overall survival (OS), and maintaining quality of life. Surgical resection followed by whole brain radiation therapy (WBRT) is the mainstay of treatment for patients with 1 to 3 operable brain metastases and with adequate performance status and control of extracranial disease. Resection plus WBRT extends the duration of survival, when compared with biopsy plus WBRT. Although adding WBRT to resection does not increase OS duration, it reduces local and distant recurrence of brain metastases. Thus, WBRT decreases the incidence of death from neurologic causes and may help maintain adequate quality of life, if the cumulative dose does not cause unacceptable neurotoxicity.

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
At present, the GliaSite® Radiation Therapy System (GliaSite RTS; IsoRay Medical) is the only device marketed in the United States for intracavitary balloon catheter brachytherapy in the brain. It includes a catheter tray with a double balloon catheter and accessories used for implantation of an aqueous saline solution of molecularly bound radioactive iodine (sodium 3-[I-125] iodo-4-hydroxybenzenesulfonate; Iotrex™) as the radiation source; and an access tray with items used for afterloading and retrieving the radioactive material. One to 3 weeks after resection and balloon implantation, the Iotrex solution is loaded through a subcutaneous port and left in for 3 to 6 days. Prescribed radiation doses are usually 40 to 60 Gy measured at 0.5 to 1.0 cm from the balloon surface. This procedure has been performed on an inpatient basis; however, feasibility of outpatient GliaSite RTS implantation has been explored.1 The GliaSite RTS received 510(k) marketing clearance from the U.S. Food and Drug Administration (FDA) in 2001, as substantially equivalent to separately marketed ventricular reservoirs and catheters, manual radionuclide applicator systems, and radionuclide sources. In 2011, the modified GliaSite RTS received 510(k) marketing clearance. FDA product code: KXK.
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Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination.

Rationale/Source
This policy was updated regularly with searches of the MEDLINE database. Most recently, the literature was reviewed through March 6, 2015.

Malignant gliomas and astrocytoma
No randomized controlled trials (RCTs) or other controlled studies were identified. All published studies were uncontrolled case series.

In 2003, Tatter et al reported on a multicenter safety and feasibility study of the GliaSite Radiation Therapy System (RTS) device for recurrent high-grade gliomas (n=21; 15 with GBM), 5 with anaplastic astrocytoma, 1 with anaplastic ODG). All patients (n=11) received first-line therapy with resection and radiation, with or without systemic chemotherapy. Time from end of first-line therapy to repeated resection for recurrent disease was not reported. Although not a primary end point, median OS was 12.7 months (95% confidence interval [CI], 6.9 to 15.3), and a Kaplan-Meier curve showed estimated OS at 1 year as just over 50%. Investigators reported no serious device-related adverse events during brachytherapy and no symptomatic radiation necrosis during follow-up.

Gabayan et al (2006) reported on a retrospective multi-institutional analysis of the GliaSite RTS device for recurrent high grade gliomas (n=95; 80 with GBM, 9 with anaplastic astrocytoma, 4 with anaplastic ODG, 1 each with a mixed anaplastic tumor or gliosarcoma). All patients received external beam radiotherapy (EBRT) after initial resection, and 55 (58%) also received systemic chemotherapy. Time from end of front-line therapy to repeated resection for recurrent disease was not reported. Fifteen patients (16%) who had previously been treated with EBRT following maximal debulking surgery were treated with GliaSite (average dose, 60 Gy) on tumor recurrence. Median OS from the time of GliaSite placement was 9.1 months (95% CI, 7.8 to 10.4), and OS at 1 year was 31.1% (95% CI, 21.2% to 41.0%). Only 2 patients experienced Radiation Therapy Oncology Group (RTOG) grade 3 toxicity attributable to radiation, and none experienced grades 4 or 5. However, 10 adverse events were attributed to surgery. The authors concluded that survival benefit was modest and that these data were similarly inconclusive to previous feasibility studies. The retrospective analysis on GliaSite did not report important prognostic factors available from the Gliadel® randomized trial (eg, median interval from first operation; cumulative radiation dose and proportion given whole brain radiotherapy [WBRT] vs local radiation vs both in first-line therapy and completeness of the second resections). The authors concluded that it is a challenge to assess survival value from these studies without better comparative evidence on demonstrably similar patient groups, preferably from a randomized comparative trial.

In 2010, Wernicke et al published a single institution, dose escalation study to investigate the safety and feasibility of GliaSite following surgical resection of localized newly diagnosed and recurrent brain tumors. The balloon was implanted during surgery in 10 consecutive patients; then 2 to 3 weeks later, aqueous solution of 125-I was introduced for times ranging from 68 to 120 hours. Median total dose was 52 Gy. Median survival for this cohort was 14 months. There were no reports of RTOG grade 3 or 4 toxicities.
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Similarly to the other studies cited, results from this trial suggest that the GliaSite RTS is relatively safe and well-tolerated in patients with localized brain tumors. However, further studies would be required to assess efficacy.

In 2011, Gobitti et al reported on 15 patients treated with GliaSite brachytherapy after surgical resection of recurrent grade 3 or 4 gliomas (10 with GBM, 4 anaplastic astrocytoma, 1 anaplastic xanthoastrocytoma). Patients were followed from 1 to 30 months. Only 2 patients survived to 30 month follow-up. Eleven patients experienced local tumor recurrence. After GliaSite brachytherapy, median OS was 13 months, and median disease-free survival was 7 months. Late radiation necrosis was experienced by 3 patients; 2 subsequently died of further complications. One patient had hemiparesis and dysphagia, which resolved over 6 months. The authors concluded that reintervention followed by GliaSite brachytherapy should not be offered as a standard treatment for recurrent high-grade glioma, because of the high rate of late complications, treatment-related deaths, and high treatment costs.

**Glioblastoma Multiforme**

No RCTs or other controlled studies were identified. All published studies were uncontrolled case series.

Johannesen et al (1999) reported on 44 newly diagnosed GBM patients implanted with intracavitary balloon catheters at resection. Two to 3 days after surgery, high dose-rate 192-Ir sources were inserted twice daily for 15 minutes over 5 to 6 days, using remote afterloading devices designed and fabricated by the investigators. Cumulative radiation doses were 60 (n=33) or 72 Gy (n=11). Median survival was 11.7 months (range, 2.7-50.9) for all patients, 12.8 months for those treated with 60 Gy, and 9.9 months for those treated with 72 Gy. OS at 1 year was 46%. Relapses occurred in 89% of patients at a median follow-up time of 8.3 months after treatment (range, 1.2-34.7). These outcomes are similar to those of conventional WBRT after resection, although investigators emphasized the shorter treatment time (1 vs 5-6 weeks) with balloon catheter brachytherapy. While the authors asserted that hospital stays were shorter (median, 21 days) and quality of life over the first 6 months was better than after conventional WBRT, they did not report data to support these claims.

In a 2007, multicenter, retrospective study, Welsh et al compiled data from 20 patients with GBM at 8 centers (median age and Karnofsky Performance Status: 59 and 89, respectively). Following maximal tumor debulking, patients were treated with GliaSite (median dose, 60 Gy) before EBRT (median dose, 110 Gy). In this cohort, average survival was 11.4 months (range, 4-29), 4 months longer than historical controls (95% CI, 0.23 to 4.9). RTOG grade 3 central nervous system toxicity was observed in 3 patients (14%). It is noteworthy that 50% of treatment failures had balloons placed 2 cm or more from the margin of the tumor. While this study may suggest that administration of increased doses (up to 100 Gy) using GliaSite is feasible and relatively well-tolerated, the authors acknowledged that putative survival advantage must be interpreted with caution. Additional studies using GliaSite in conjunction with EBRT following surgery for newly diagnosed GBM would be required to adequately assess safety and efficacy.

In a 2005 study (n=24) on recurrent GBM performed at Johns Hopkins Medical Center, investigators reported results to be inconclusive. Front-line therapy included surgery followed by EBRT. Time from primary resection (or from end of primary treatment) to recurrence was not reported. Median OS was 23.3
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months (range, 9.3–64.1 months) from diagnosis of the primary tumor, and 9.1 months (range, 1.3-23.6 months) from GliaSite RTS treatment. Kaplan-Meier analyses showed OS at 1 year to be approximately 33%. GliaSite was relatively well-tolerated in this cohort with few serious adverse events. Acute adverse effects were reportedly mild; 1 patient experienced mild nausea and vomiting, and 10 experienced mild to moderate headaches. Late complications included 1 case of global aphasia and 2 incidents of symptomatic necrosis.

In 2013, Waters et al reported on a retrospective review of 11 patients with newly diagnosed glioblastoma who received brain brachytherapy 2 to 3 days postsurgical resection before EBRT and temozolomide. Brachytherapy was delivered at 45 to 60 Gy with GliaSite in 9 patients and with MammoSite in 2 patients. While progression-free survival trended toward improvement at 6 months, OS did not differ from historical controls.

Brain Metastasis From Other Primary Solid Malignancies

No RCTs were identified. However, in 2006, Rogers et al published a multicenter, nonrandomized comparative study including 71 patients with 1 to 3 brain metastases from a solid tumor of distant origin. Enrolled patients received either GliaSite (n=62) or standard brachytherapy with lotrex solution (n=54). Outcomes were analyzed without an intention-to-treat model. Primary malignancies included non-small-cell lung (54%) and gastrointestinal tract (13%) cancers, melanoma (13%), renal carcinoma (6%), and others (15%). While most patients (57%) had only brain metastases, many (43%) also had extracranial metastases. Prior therapies varied widely and included no treatment (22%), surgery (31%), surgery and radiation (33%), or surgery in addition to chemotherapy followed by radiation (24%). Estimated local control at 1 year was 79%, and median duration of local control exceeded 16.5 months. Median OS was 10 months (95% CI, 7.8 to 15), OS at 1 year was 40%, and median duration of functional independence was 10 months (95% CI, 7.3 to 20.8). Symptomatic imaging changes led to repeated operation in 13 patients, 9 of whom had radiation necrosis, 2 had mixed tumor and necrosis, and 2 had tumor recurrence only. A total of 9 grade 3 and 1 grade 4 toxicities were reported in the treated population.

Investigators indirectly compared the rate of local control in the GliaSite-treated population: 79% with historical data showing 80% to 90% local control after resection plus WBRT and only 40% after resection only. However, an accompanying editorial cautioned that the rate of new metastases elsewhere in the brain was 50% by 1 year after treatment and attributes this to omission of WBRT. The editorial also stressed the need for direct comparative evidence to determine whether neurocognitive function and quality of life are adequately maintained for longer durations with initially focal treatment and WBRT at recurrence or with focal treatment immediately combined with WBRT.

Safety Considerations

Overall, adverse events with GliaSite do not differ greatly from those observed with other brain brachytherapy techniques; however, in 2008, Adkison et al reported a case in which linens of a patient with the GliaSite implant were contaminated with radiation. Recovery studies confirmed that systemic absorption is greater than anticipated. Adkison et al concluded that precaution with a Foley catheter should be taken in patients with urinary incontinence. Some cases of brain hemorrhage have been reported, so careful coagulation control is critical.
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Chino et al examined feasibility of outpatient GliaSite brachytherapy in 37 patients. Rather than overnight hospitalization, patients were released after the treatment sessions. Although the study was small and ultimately inconclusive, the outpatient approach did not appear to increase adverse events and seemed to be generally well tolerated.

Summary

Intracavitary balloon catheter brain brachytherapy is an approach to localized radiation therapy delivered with an inflatable balloon catheter in the treatment of malignant brain lesions. To date, no standard medical care is established for primary brain malignancies or brain metastases of solid tumors, and there is insufficient evidence, particularly from controlled trials, demonstrating that intracavitary balloon brachytherapy extends the duration of survival, time-to-relapse, quality of life, or time-to-progression. Therefore, the use of intracavitary balloon brachytherapy for brain cancer and brain metastases of solid tumors is considered investigational.

References

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10/02/2014 Medical Policy Committee review
01/01/2015 Coding Update
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
12/03/2015 Medical Policy Committee review
12/16/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 12/2016

Coding
The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®), copyright 2014 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:
A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means
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of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

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