Name of Policy:
Intracavitary Balloon Catheter Brain Brachytherapy for Malignant Gliomas or Metastasis to the Brain

Policy #: 418       Latest Review Date: April 2014
Category: Therapy       Policy Grade: B

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. 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 that patient’s illness, injury or disease.
Description of Procedure or Service:
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.

At present, the GliaSite® radiation therapy system (GliaSite® RTS; IsoRay Medical, Inc. 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; an aqueous saline solution of molecularly bound radioactive iodine [sodium 3-(¹²⁵I)iodo-4-hydroxybenzenesulfonate; Iotrex™] as the radiation source; and an access tray with items used for afterloading and retrieving the radioactive material. One to three weeks after resection and balloon implantation, the Iotrex™ solution is loaded through a subcutaneous port and left in for three to six days. Prescribed radiation doses are usually 40–60 Gy measured at 0.5–1.0 cm from the balloon surface. The GliaSite® RTS received 510(k) marketing clearance from the U.S. Food and Drug Administration (FDA), 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.

Malignant Gliomas
Diffuse fibrillary astrocytoma is the most common glial brain tumor in adults. It is classified histologically into three Grades: Grade II astrocytoma, Grade III anaplastic astrocytoma, and Grade IV glioblastoma multiforme (GBM). Oligodendrogliomas (ODG) 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 ten years versus two to three years. Also, ODGs apparently are more chemosensitive than astrocytomas. GBM, the most aggressive and chemoresistant astrocytoma, has survival times less than two 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 particularly poor outcome since 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, and vincristine. The most common regimen combines procarbazine, lomustine (also known as CCNU), and vincristine (PCV). A biodegradable polymer wafer impregnated with carmustine (Gliadel®; Guilford Pharmaceuticals, Inc.) also can be implanted into the surgical cavity as an adjunct to surgery.
Brain Metastasis from Other Primary Malignancies

Intracranial metastases are a frequent occurrence, seen at autopsy in 10%–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, and maintaining quality of life. Surgical resection followed by whole brain radiation therapy (WBRT) is the mainstay of treatment for patients with one to three 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 overall survival duration, it reduces local and distant recurrence of brain metastases. Thus, WBRT decreases the incidence of death from neurological causes, and may help maintain adequate quality of life, if the cumulative dose does not cause unacceptable neurotoxicity.

Policy:

**Intracavitary balloon catheter brain brachytherapy does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage, alone or as part of a multimodality treatment regimen, for primary or recurrent malignant gliomas, and is considered **investigational**.

**Intracavitary balloon catheter brain brachytherapy does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage, alone or as part of a multimodality treatment regimen, for metastasis to the brain from primary malignancies outside the brain, and is considered **investigational**.

*Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.*

**Key Points:**

**Malignant glioma and astrocytoma**

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

Gabayan et al reported on a retrospective multi-institutional analysis of the GliaSite® RTS device for recurrent high-grade gliomas in 2006 (n=95; 80 with GBM, nine with anaplastic astrocytoma, four with anaplastic ODG, one each with a mixed anaplastic tumor or gliosarcoma). All patients received external beam radiation after initial resection, and 55 (58%) also received systemic chemotherapy. Twenty patients (21%) had Gliadel® wafers placed at the time of surgery for the primary tumor. Time from end of first-line therapy to repeated resection for recurrent disease was not reported. Fifteen patients (16%) had Gliadel® wafers placed with implantation of the balloon catheter, and an unreported number had additional chemotherapy. Median overall survival was 9.1 months (95% CI: 7.8, 10.4), and overall survival at one year was 31.1% (95% CI: 21.2%, 41.0%). Only two patients experienced Radiation Therapy Oncology Group (RTOG) Grade 3 toxicity attributable to radiation; 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 (e.g., median interval from first operation; cumulative radiation dose and proportion given whole-brain radiation therapy [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.

Wernicke and colleagues conducted 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 ten consecutive patients; then two to three 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. Similarly to the other studies cited, results from this trial suggest that the GliaSite® radiation therapy system is relatively safe and well-tolerated in patients with localized brain tumors. However, further studies would be required to assess efficacy.

In 2011, Gobitti and colleagues reported on 15 patients treated with GliaSite® brachytherapy after surgical resection of recurrent Grade 3 or 4 gliomas. Patients were followed from 1-30 months. Only two patients survived to 30 months follow-up. Eleven patients experienced local tumor recurrence. After GliaSite® brachytherapy, median overall survival was 13 months and median disease-free survival was seven months. Late radiation necrosis was experienced by three patients; two subsequently died of further complications. One patient had hemiparesis and
dysphagia, which resolved over six months. The authors concluded that re-intervention 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**

Johannesen et al reported a Phase I/II study on 44 newly diagnosed glioblastoma multiforme (GBM) patients implanted with intracavitary balloon catheters at resection. Two to three days after surgery, high dose-rate 192-Ir sources were inserted twice daily for 15 minutes over five to six days, using remote after-loading 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 to 50.9 months) for all patients, 12.8 months for those treated with 60 Gy, and 9.9 months for those treated with 72 Gy. Overall survival at one year was 46%. Relapses occurred in 89% of patients at a median follow-up time of 8.3 months after treatment (range: 1.2 to 34.7 months). These outcomes are similar to those of conventional WBRT after resection, although investigators emphasized the shorter treatment time (1 vs. 5 to 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 six months was better than after conventional WBRT, they did not report data to support these claims.

In the multicenter, retrospective study performed by Welsh et al, data were compiled from eight centers on 20 patients with GBM patients with median age and Karnofsky performance status of 59 and 89, respectively. Following maximal tumor debulking, patients were treated with GliaSite® (median dose 60 Gy) prior to external-beam radiation (median dose 110 Gy). In this cohort, average survival was 11.4 months (range 4-29), four months longer than historical controls (95% CI: 0.23–4.9). RTOG Grade-3 central nervous system toxicity was observed in three patients (14%). It is noteworthy that 50% of treatment failures had the balloons placed 2cm 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 acknowledge that putative survival advantage must be interpreted with caution. Additional studies using GliaSite® in conjunction with external-beam radiation following surgery for newly diagnosed GBM would be required to adequately assess safety and efficacy.

In a clinical trial (n=24) on recurrent GBM performed at Johns Hopkins Medical Center, investigators reported results to be inconclusive. Front-line therapy included surgery followed by external-beam radiation. Time from primary resection (or from end of primary treatment) to recurrence was not reported. Median OS was 23.3 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 one year to be approximately 33%. GliaSite® was relatively well-tolerated in this cohort with few serious adverse events. Acute adverse effects were reportedly mild; one patient experienced mild nausea and vomiting, and ten experienced mild to moderate headaches. Late complications included one case of global aphasia and two incidents of symptomatic necrosis.

In 2013, Waters et al reported on a retrospective review of 11 patients with newly diagnosed glioblastomas who received brain brachytherapy two to three days post-surgical resection prior
to external beam radiation therapy and temozolomide. Brachytherapy was delivered at 45 to 60 Gy with GliaSite in nine patients and with MammoSite in two patients. While progression free survival trended toward improvement at six months, overall survival did not differ from historical controls.

Finally, Payne et al. published a case report of one patient with GBM undergoing implantation with two brachytherapy balloons; however, there are no additional studies assessing the two-balloon approach.

**Brain metastasis from other primary solid malignancies**

A prospective, multicenter, Phase II trial enrolled 71 patients with one to three brain metastases from a solid tumor of distant origin. Patients enrolled received either GliaSite® (n=62) or standard brachytherapy with Iotrex 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%). The investigators estimated local control at one year was 79%, and the median duration of local control was greater than 16.5 months. Median OS was ten months (95% CI: 7.8–15), OS at 1 year was 40%, and median duration of functional independence was ten months (95% CI: 7.3–20.8). Symptomatic imaging changes led to repeated operation in 13 patients, nine of whom had radiation necrosis, two had mixed tumor and necrosis, and two had tumor recurrence only. A total of nine Grade-3 and one 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 80–90% local control after resection plus WBRT and only 40% after resection only. However, an accompanying editorial cautions that the rate of new metastases elsewhere in the brain was 50% by one year after treatment and attributes this to omission of WBRT. The editorial also stresses 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® are not greatly varied from those observed with other brain brachytherapy techniques; however, in 2008, Adkison and colleagues 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.

Chino and colleagues 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 are no clinical data available to provide convincing evidence 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 remains investigational.

**Practice Guidelines and Position Statements**
The National Comprehensive Cancer Network (NCCN) guidelines for Central Nervous System (CNS) Cancers mention in the Discussion Section that brachytherapy is one of several treatment options used by radiation oncologists. However, the terms GliaSite, intracavitary, or balloon (related to CNS cancers) are not mentioned in these guidelines.

**Key Words:**
Brachytherapy, Brain, Intracavitary, GliaSite, I-125 Iotrex™

**Approved by Governing Bodies:**
GliaSite® RTS

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

**Coding:**
CPT Codes:
There is not specific CPT code for this procedure.

HCPCS:
A9527 Iodine I-125 sodium iodide solution, therapeutic, per mCi
References:

Policy History:
Medical Policy Group, March 2010 (3)
Medical Policy Administration Committee, April 2010
Available for comment April 7-May 21, 2010
Medical Policy Group, April 2011 (3): Updated Key Points and References
Medical Policy Group, April 2012 (3): 2012 Updates-Key Points and References
Medical Policy Panel, April 2013
Medical Policy Group, April 2013 (3): 2013 Updates to Key Points and References; no changes in policy statement
Medical Policy Panel, April 2014
Medical Policy Group, April 2014 (3): 2014 Updates to Key Points & References; no change in policy statement
Medical Policy Group, June 2014 (3): Updated policy with link to CareCore National© medical policies effective August 1, 2014
Medical Policy Administration Committee, June 2014
Available for comment June 16 through July 31, 2014
Medical Policy Group, July 2014: Removed CareCore link. Transfer to CareCore is on hold until further notice. The policy has been returned to FINAL.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.