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

DISCLAIMER

Our medical policies are designed for informational purposes only and are not an authorization, explanation of benefits or a contract. Receipt of benefits is subject to satisfaction of all terms and conditions of the coverage. Medical technology is constantly changing, and we reserve the right to review and update our policies periodically.

POLICY

Intracavitary balloon catheter brain brachytherapy is considered investigational, alone or as part of a multimodality treatment regimen, for primary or recurrent malignant brain tumors.

Intracavitary balloon catheter brain brachytherapy is considered investigational, alone or as part of a multimodality treatment regimen, for metastasis to the brain from primary solid tumors outside the brain.

POLICY GUIDELINES

There are no CPT codes specific to implantation of this type of balloon catheter. It is possible that the provider may use CPT code 64999 (unlisted procedure, nervous system).

The administration of the radiation source would likely be coded using one of the CPT codes for radiation source application (77761-77763) or remote afterloading of high-dose brachytherapy (77785-77787).

There is a HCPCS code specific to the radiation solution used in this procedure:

A9527 Iodine I-125 sodium iodide solution, therapeutic, per mci.

BENEFIT APPLICATION

BLUECARD/NATIONAL ACCOUNT ISSUES

State or federal mandates (eg, Federal Employee Program) may dictate that certain U.S. Food and Drug Administration–approved devices, drugs, or biologics may not be considered investigational, and thus these devices may be assessed only by their medical necessity.

BACKGROUND

BRAIN TUMORS

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. Oligodendrogliomas 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 vs 2 to 3 years. Also, oligodendrogliomas apparently are more chemosensitive than astrocytomas. The most aggressive and chemoresistant astrocytoma, glioblastoma multiforme has survival times of less than 2 years for most patients.

**Treatment**

Treatment of primary brain tumors begins with surgery with curative intent or optimal tumor debulking, usually followed by radiotherapy 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, 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, vincristine, and single or multiagent therapy with temozolomide. A biodegradable polymer wafer impregnated with carmustine (Gliadel® Wafer; Guilford Pharmaceuticals) 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 glioblastoma multiforme.

**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**

Treatment goals in these patients include local control of existing metastases, regional control to prevent the growth of undetected metastases, extending the duration of overall survival, and maintaining quality of life. Surgical resection followed by whole-brain radiotherapy (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 compared with biopsy plus WBRT. Although adding WBRT to resection does not increase the duration of overall survival, it reduces local and distant recurrence of brain metastases. Thus, WBRT decreases the incidence of death from neurologic causes and may help maintain an adequate quality of life, if the cumulative dose does not cause unacceptable neurotoxicity.

**INTRACAVITARY BALLOON CATHETER BRAIN BRACHYTHERAPY**

Intracavitary balloon catheter brain brachytherapy is localized temporary high-dose radiotherapy 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.

**Safety Considerations**

Overall, adverse events with GliaSite do not differ greatly from those observed with other brain brachytherapy techniques; however, Adkison et al (2008) reported a case in which linens of a patient
with the GliaSite implant were contaminated with radiation.^{1} 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. Gerber et al (2007) reported cases of brain hemorrhage have, suggesting the need for careful coagulation control.^{2}

REGULATORY STATUS
In 2001, the GliaSite® Radiation Therapy System (GliaSite® RTS; IsoRay Medical) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process (K003206). FDA determined that this device was substantially equivalent to separately marketed ventricular reservoirs and catheters, manual radionuclide applicator systems, and radionuclide sources.

In 2011, a modified GliaSite® RTS was cleared for marketing by FDA through the 510(k) process (K111931). GliaSite® RTS 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 gray measured at 0.5 to 1.0 cm from the balloon surface. This procedure has been performed on an inpatient basis.

In December 2013, CESITRX (Liquid Cesium131 solution) was cleared for marketing by FDA through the 510(k) process (K132996) for use with GliaSite RTS.

FDA product code: KXK.

RATIONALE
This evidence review was created in February 2007 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through May 7, 2018.

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Because primary brain tumors and brain metastases from other tumors have poor prognoses and are treatment-resistant, nonrandomized comparative studies and uncontrolled studies may provide useful information on health outcomes.
PRIMARY BRAIN TUMORS

Clinical Context and Therapy Purpose
The purpose of intracavitary balloon catheter brain brachytherapy in patients who have primary 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 intracavitary balloon catheter brain brachytherapy improves the net health outcome in individuals with primary brain tumors?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals with primary brain tumors.

Interventions
The therapy being considered is intracavitary balloon catheter brain brachytherapy.

Comparators
The following therapies are currently being used: other forms of radiotherapy.

Outcomes
The general outcomes of interest are overall survival (OS), recurrence-free survival, and symptom reductions (eg, headaches, seizures, behavioral changes).^3

Timing
Depending on the glioma staging, the 5-year prognosis for adults in this patient population is less than 6% (median survival, 15 months). Generally, the 5-year adult survival rate for brain tumors is less than 35%.^4

Setting
Brachytherapy usually requires brief hospitalization while radioactive seeds are implanted under anesthesia. More than 1 treatment may be required.

Malignant Gliomas and Astrocytoma
No RCTs or other controlled studies were identified. All published studies are uncontrolled case series.

Tatter et al (2003) 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 glioblastoma multiforme [GBM], 5 with anaplastic astrocytoma, 1 with anaplastic oligodendrogliomas).^5 All patients 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 months), and a Kaplan-Meier curve showed the estimated OS rate 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 oligodendrogliomas, one each with a mixed anaplastic tumor or gliosarcoma).^6 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 (16%) patients who had previously been treated with EBRT following maximal debulking surgery were treated with GliaSite RTS (average dose, 60 gray [Gy]) on tumor recurrence. Median OS from the time of GliaSite placement was 9.1 months (95% CI, 7.8 to 10.4 months), and the OS rate at 1 year was 31.1% (95% CI, 21.2% to 41.0%). Only 2 patients experienced Radiation Therapy Oncology Group grade 3 toxicity attributable to radiation, and none experienced grade 4 or 5 toxicity. However, 10 adverse events were attributed to surgery. The authors concluded that survival benefit was modest and that, similar to previous feasibility studies, these data were inconclusive. The retrospective analysis on GliaSite did not report important prognostic factors available from the Gliadel randomized trial (eg, median interval from the 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). Authors found it challenging to assess survival value from these studies without better comparative evidence on demonstrably similar patient groups, preferably from a randomized comparative trial.

Wernicke et al (2010) reported on a single-institution, dose-escalation study investigating the safety and feasibility of GliaSite after 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, an aqueous solution of iodine 125 was introduced for times ranging from 68 to 120 hours. The median total dose was 52 Gy. Median survival for this cohort was 14 months. There were no reports of Radiation Therapy Oncology Group grade 3 or 4 toxicities. Similarly to the other studies cited, results from this trial suggested that the GliaSite RTS is relatively safe and well-tolerated in patients with localized brain tumors.

Gobitti et al (2011) reported on 15 patients treated with GliaSite brachytherapy after surgical resection of recurrent grade 3 or 4 gliomas (10 with GBM, 4 anaplastic astrocytomas, 1 anaplastic xanthoastrocytoma). Patients were followed for 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; two 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.

No published studies using liquid cesium 131 for this indication were identified.

**Section Summary: Malignant Gliomas and Astrocytoma**

The evidence for the use of intracavitary balloon brain brachytherapy for malignant gliomas and astrocytomas consists of early-phase feasibility and dose-ranging studies, a small case series, and a retrospective review. There are no published RCTs. The evidence does not support conclusions on the effects of the technology on health outcomes.

**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 iridium 192 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 months) for all patients, 12.8 months for those treated with
Intracavitary Balloon Catheter Brain Brachytherapy for Malignant Gliomas or Metastasis to the Brain

60 Gy and 9.9 months for those treated with 72 Gy. The OS rate at 1 year was 46%. Relapses occurred in 89% of patients at a median follow-up of 8.3 months after treatment (range, 1.2-34.7 months). These outcomes are similar to those of conventional WBRT after resection, although investigators emphasized the shorter treatment time (1 week vs 5-6 weeks) with balloon catheter brachytherapy. While claiming that hospital stays were shorter (median, 21 days) and quality of life over the first 6 months was better than after conventional WBRT, the authors did not report data to support these claims.

In a multicenter, retrospective study, Welsh et al (2007) compiled data from 20 patients with GBM at 8 centers (median age, 59 years; median Karnofsky Performance Status score, 89). 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 months), 4 months longer than historical controls (95% CI, 0.23 to 4.9 months). Radiation Therapy Oncology Group grade 3 central nervous system toxicity was observed in 3 (14%) patients. It is noteworthy that 50% of treatment failures had balloons placed 2 cm or more from the margin of the tumor. While this study might 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 cautiously. Additional studies using GliaSite with EBRT following surgery for newly diagnosed GBM would be required to assess safety and efficacy adequately.

In a small study (N=24) on recurrent GBM performed at university medical center, Chan et al (2005) reported results to be inconclusive. Front-line therapy included surgery followed by EBRT. Time from primary resection (or from the 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 a 1-year OS rate 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 a case of global aphasia and 2 incidents of symptomatic necrosis.

Waters et al (2013) retrospectively reviewed 11 patients with newly diagnosed GBM who received brain brachytherapy 2 to 3 days after surgical 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.

No published studies using liquid cesium 131 for this indication were identified.

**Section Summary: Glioblastoma Multiforme**
The evidence for the use of intracavitary balloon brain brachytherapy to treat GBM is limited to case series. The evidence is insufficient to determine the effects of the technology on health outcomes.

**BRAIN METASTASES FROM OTHER PRIMARY SOLID MALIGNANCIES**

**Clinical Context and Therapy Purpose**
The purpose of intracavitary balloon catheter brain brachytherapy in patients who have metastases to the brain from other 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 intracavitary balloon catheter brain brachytherapy improves the net health outcome in individuals with metastases to the brain from other tumors?
The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest is individuals with metastases to the brain from other tumors (eg, non-small-cell lung cancer, renal cell carcinoma, melanoma).

**Interventions**
The therapy being considered is intracavitary balloon catheter brain brachytherapy.

**Comparators**
The following therapies are currently being used: other forms of radiotherapy.

**Outcomes**
The general outcomes of interest are OS, recurrence-free survival, and symptom reductions (eg, headaches, seizures, cognitive changes).

**Timing**
Given the prognosis of this patient population, follow-up to 5 years is rare (<35%).

**Setting**
Brachytherapy usually requires brief hospitalization while radioactive seeds are implanted under anesthesia. More than 1 treatment may be required.

**Nonrandomized Studies**
No RCTs were identified. However, Rogers et al (2006) published a multicenter, nonrandomized noncomparative study including 71 patients with 1 to 3 brain metastases from a solid tumor of distant origin. Enrolled patients received placement of the GliaSite balloon followed by installation of aqueous iodine-125 radiotherapy solution with the prescribed total dose for each patient of 60 Gy at a 1-cm depth to be delivered at a rate of 40 to 60 centigray per hour. The primary study end point was the 1-year local control rate. 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 plus radiotherapy (33%), or surgery plus chemotherapy followed by radiotherapy (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 months), OS rate at 1 year was 40%, and median duration of functional independence was 10 months (95% CI, 7.3 to 20.8 months). Symptomatic imaging changes led to repeated surgeries in 13 patients, 9 of whom had radiation necrosis, 2 had mixed tumor and necrosis, and 2 had tumor recurrence only. Nine grade 3 and 1 grade 4 toxicities were reported in the treated population.

Investigators indirectly compared the local control rate 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 attributed this to the omission of WBRT. The editorial also emphasized 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.

No published studies using liquid cesium 131 for this indication were identified.
Section Summary: Brain Metastases From Other Primary Solid Tumors
The evidence for the use of intracavitary balloon brain brachytherapy to treat brain metastases from other tumors is limited to a nonrandomized, single-arm study. The relevance of outcomes indirectly demonstrating local control of 79% at 1 year is confounded by the varying radiosensitivity of the tumors, and OS was impacted by the rate of extracranial metastatic disease. The evidence does not support conclusions on the effects of the technology on health outcomes.

SUMMARY OF EVIDENCE
For individuals who have primary newly diagnosed or recurrent brain tumors who receive intracavitary balloon catheter brain brachytherapy as an adjunct to resection, the evidence includes early-phase feasibility and dose-ranging studies, case series, and a retrospective review. Relevant outcomes are overall survival, symptoms, and treatment-related morbidity. The evidence is limited by the lack of RCTs and comparators in nonrandomized studies. The heterogeneity of tumor metastatic tumor types limits the interpretation of reported short-term survival outcomes. Long-term outcome studies have not been reported. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have metastases to the brain from other tumors who receive intracavitary balloon catheter brain brachytherapy as an adjunct to resection, the evidence includes a multicenter, nonrandomized, single-arm study. Relevant outcomes are overall survival, symptoms, and treatment-related morbidity. The evidence is limited by the lack of RCTs or comparators in nonrandomized studies. The only outcomes data reported have been the local control rates at 1 year. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS
National Comprehensive Cancer Network guidelines (v.1.2018) for central nervous system cancers mention brachytherapy as one of several treatment options used by radiation oncologists. However, the terms GliaSite, intracavitary, or balloon (related to central nervous system cancers) are not mentioned in these guidelines.

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
A search of ClinicalTrials.gov in June 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

REFERENCES

**CODES**

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

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### Type of Service
- Surgical, removal, infusion device, cranium, code by approach (external, open, percutaneous, percutaneous endoscopic)
- Administration of liquid brachytherapy radioisotope, percutaneous
- Administration of liquid brachytherapy radioisotope, via natural or artificial opening

### Place of Service

### POLICY HISTORY

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