Name of Policy:
Endobronchial Brachytherapy

Policy #: 251       Latest Review Date: February 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:
Endobronchial brachytherapy is the delivery of radiation therapy directly to endobronchial lesions either intraluminally or interstitially using permanently implanted radioactive seeds or a temporary afterloading implant. The technique permits targeted radiation while minimizing exposure to surrounding radiosensitive structures, such as normal lung, heart, and spinal cord.

Endobronchial brachytherapy has been most investigated as a palliative treatment of obstructing primary or metastatic tumors, particularly in non-small-cell lung cancer (NSCLC). There is also experience using endobronchial brachytherapy as a tool in curative treatment for some primary bronchial and tracheal tumors. Two to four fractions delivered weekly is a typical schedule. The most serious complications described for endobronchial brachytherapy are massive hemoptysis, formation of tracheoesophageal fistulas, bronchospasm, bronchial stenosis, and radiation bronchitis.

In the outpatient setting, the patient receives local anesthesia and monitored sedation. A flexible bronchoscope is passed transnasally; a separate port on the bronchoscope allows passage of the afterloading catheter to the target lesion. Once the catheter is placed, the radioisotope can be administered by the high-dose radiotherapy afterloading machine. Patients with potential airway compromise due to bleeding may require treatment with a rigid bronchoscope, which requires general anesthesia and frequently an overnight stay.

Endobronchial brachytherapy represents one approach to the local treatment of endobronchial lesions. Other technologies include electrocoagulation, cryosurgery, laser resection, endosurgery, and endobronchial stent placement. In some instances, the therapies may be used together, such as using laser therapy for initial debulking followed by brachytherapy.

Policy:
Endobronchial brachytherapy meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage in the following clinical situations:

- In patients with primary endobronchial tumors who are not otherwise candidates for surgical resection or external-beam radiation therapy due to comorbidities or location of the tumor; or
- As a palliative therapy for airway obstruction or severe hemoptysis in patients with primary, metastatic, or recurrent endobronchial tumors

Other applications of endobronchial brachytherapy are investigational including, but not limited to, its use as a radiation “boost” to curative external-beam radiotherapy, as treatment for asymptomatic recurrences of non-small-cell lung cancer, or in the treatment of hyperplastic granulation tissue.

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:
Endobronchial brachytherapy is used as both palliative treatment and curative treatment; either alone or in combination with other modalities such as surgery, external-beam radiation, or other endoscopic interventions.

Endobronchial brachytherapy as palliative treatment
Many patients with non-small-cell lung cancer (NSCLC) are initially treated with external-beam radiation therapy but ultimately experience local recurrence. Unfortunately, many are not candidates for further external-beam radiation therapy due to the limited tolerance of normal tissue. If symptoms persist following external-beam radiation, endobronchial brachytherapy is well accepted as a short-term palliation for such symptoms as hemoptysis, cough, dyspnea, and resolution of obstructive atelectasis or pneumonitis. A European prospective study reported on 270 patients who had previously received radiation therapy and subsequently were given high-dose brachytherapy resulting in a total response rate of 80% for symptoms of dyspnea, cough, hemoptysis, and postobstructive pneumonia with a median duration of palliation of five months with a range of two to 14 months. In a summary of studies of palliative endobronchial brachytherapy between 1985 and 1994, Villanueva et al reported effective palliation in 60% to 100% of patients. The median survival of these patients is typically less than nine months.

A 2008 Cochrane review of palliative endobronchial brachytherapy for NSCLC, updated in 2012, analyzed 13 randomized, controlled trials (RCTs) but could not combine them into a meta-analysis because of heterogeneity in the doses of radiotherapy delivered, patient characteristics, and outcomes measured. The authors concluded that external-beam radiation therapy alone is still more effective for palliation of symptoms than endobronchial brachytherapy alone. Their findings did not provide conclusive evidence that endobronchial brachytherapy plus external-beam radiation therapy improved symptom relief over external-beam radiation alone, nor did it improve complication rates or extend survival. In summary, the authors were unable to provide conclusive evidence to recommend endobronchial brachytherapy as an add-on to first-line external-beam radiation therapy, chemotherapy, or Nd-YAG laser palliative treatment. For patients previously treated by external-beam radiation who are still symptomatic, endobronchial brachytherapy may be considered an option.

In agreement with the Cochrane review, a 2006 prospective randomized trial from India with just 45 patients suggested that endobronchial brachytherapy alone and endobronchial brachytherapy with external radiation had similar efficacy and safety profiles in the palliative management of NSCLC.

Also in agreement with the Cochrane review, Ung et al conducted a 2006 systematic review of endobronchial brachytherapy in the palliative treatment of NSCLC with 29 studies and six randomized trials. The authors concluded that external-beam radiation therapy alone is more
effective than endobronchial brachytherapy alone for symptom palliation in previously untreated patients. In contrast to the Cochrane review though, the Ung review concluded that endobronchial brachytherapy with external beam radiation seems to provide better symptom relief than external beam radiation alone, yet their final recommendation is to only use endobronchial brachytherapy with symptomatic recurrent endobronchial obstruction following external-beam radiation.

Most studies evaluate the use of endobronchial brachytherapy in lung cancer, but a 2007 French study reported on the use of endobronchial brachytherapy in a small number of patients with endobronchial metastases secondary to colorectal carcinomas. All patients had primary resection of the colorectal carcinoma then seven received intrabronchial therapies including brachytherapy and seven did not. Patients receiving intrabronchial therapies had a median survival of 55.7 months versus 12.7 months for the controls. It is difficult to draw conclusions from this small study, larger trials are still needed.

Ozkok et al published a case series from Turkey on the use of high dose rate endobronchial brachytherapy for palliation of symptoms for 158 patients in three patient groups. Group A consisted of 43 patients with stage IIIA and IIIB NSCLC who received endobronchial brachytherapy in combination with external beam radiation; Group B consisted of 74 previously untreated patients with incurable, locally advanced lung cancer; and Group C consisted of 41 patients with symptomatic endobronchial recurrences and who had previously been irradiated with full doses of radiation therapy. Participants in Group A were from a previously reported prospective trial; data from these participants were reanalyzed for palliation of symptoms in the current report. Not all patients received the intended number of fractions due to patient refusal or deterioration in performance status. A few patients required more than the prescribed doses due to repetitive obstructive symptoms. Response rates for cough, dyspnea, and hemoptysis were measured by the Speiser symptom index scoring system. The response rates in Group A were 58% for cough (30% complete response), 77% for dyspnea (76% complete response), and 100% for hemoptysis (92% complete response). Groups B and C had response rates of 57% and 55% for cough and 90% and 78% for dyspnea, respectively. Eighteen patients (11%) died of hemoptysis, with a median time to event of seven months. Significant prognostic factors for fatal hemoptysis were use of brachytherapy intended as a treatment (as opposed to strictly palliation, p<0.001), total radiobiological equivalent dose (p<0.001) and the number of high dose rate endobronchial brachytherapy fractions (p<0.001). The authors conclude that high dose rate endobronchial brachytherapy is effective for the palliation of symptoms related to inoperable lung cancer, either alone or in combination with external-beam radiation. They caution that optimal dose, fractionation, and combination schedule with external-beam radiation are yet to be determined. Further, they state that any benefit must be weighed against potentially serious treatment-related morbidity or mortality. Without a comparison group, it is not possible to draw conclusions from this case series.

Although endobronchial brachytherapy is often used to palliate hemoptysis, historically, there has been concern about an observed association between treatment with endobronchial brachytherapy and fatal hemoptysis. The largest study was a retrospective review of 938 patients treated with external irradiation and/or endobronchial brachytherapy for inoperable NSCLC. In this study, 101 patients (10.8%) died from massive hemoptysis; 78 of those who died (77%) had
clinical or radiologic evidence of tumor progression, and 23 (23%) did not. On multivariate analysis, intrabronchial tumor extension in the main bronchus, hemoptysis before radiotherapy, and tumor location in the upper bronchus were independently associated with massive hemoptysis. A dose-response relationship between fraction dose and massive hemoptysis also was found; in all subgroups, higher incidence of massive hemoptysis was seen after fraction dose of 15 Gy. These data were largely consistent with data published by Hennequin et al who reported that hemoptysis was most likely due to disease progression, with brachytherapy facilitating bleeding, rather than a direct complication of brachytherapy itself. The authors noted that for tumors located in the upper lobes, brachytherapy may be causal. Tumor location was cited as the most important factor in predicting pulmonary hemoptysis in a 1991 case series reported by Bedwinek et al in which 32% of patients died of massive hemoptysis after brachytherapy.

Dagnault et al reported a retrospective review of 81 patients who were treated with brachytherapy for symptom palliation due to endobronchial primary lung tumors or metastases. Between 2002 and 2007, 81 patients who were not candidates for surgery or external radiation because of poor respiratory function, medical comorbidities, or previous treatment with thoracic radiation or surgery, were treated at a single institution. Mean patient age was 66 years (range, 39-87). Previous treatment comprised surgical resection of the primary tumor in 58% of patients, lung radiotherapy in 44%, and chemotherapy in 41%. After endobronchial brachytherapy, patients were followed until death or loss to follow-up. Patient characteristics included 59 (73%) with a lung primary and the remainder with metastatic disease, including primary colorectal cancer (13%), kidney, gynecologic, or head and neck cancers (4% each), and other cancers (2%). Presenting symptoms included dyspnea (66%), cough (47%), hemoptysis (28%), and no symptoms (6%). After brachytherapy, major symptomatic improvement was seen in most patients: Dyspnea improved during or shortly after the end of treatment in 85% of patients; hemoptysis stopped in all 23 patients; cough improved in 77% of patients; and 18% remained stable. At six weeks’ follow-up, 72% of tumors were evaluable for bronchoscopic response. A visible bronchoscopic response was evident in 77 patients; for 42 (52%) of 81 patients, the tumor shrank significantly during treatment. Median survival was 14.7 months; local progression-free survival was 77% at 12 months and 64% at 24 months. For comparison, the authors stated that survival for most patients with inoperable endobronchial tumors or metastasis was less than six months. The incidence of complications was low, and all complications resolved.

Guarnaschelli et al reviewed treatment outcomes of 52 patients with recurrent endobronchial tumors who underwent palliative high-dose-rate endobronchial brachytherapy between 1995 and 2005 at one institution. Objective response was assessed by bronchoscopy and chest computed tomography and subjective clinical response by patient reports. All patients had histologically proven bronchogenic carcinoma, recurrent or persistent symptoms (hemoptysis, cough, dyspnea, or post-obstructive pneumonia), previous definitive external-beam radiotherapy, and bronchoscopic evidence of endobronchial obstruction. Mean patient age was 63 years (range, 41-83) and 37% of patients were women. Tumor histology was non-small cell in 77% of patients, small cell in 13%, adenoid cystic in 2%, and metastatic in 2%. Patient symptoms before brachytherapy included dyspnea upon exertion (79%), cough (89%), hemoptysis (62%), wheezing (52%), dysphagia (8%), chest pain (15%), and shortness of breath (83%). Symptomatic improvement was defined as significant if there was improvement in two or more symptoms and
mild if only one symptom improved. Forty-eight patients (92%) showed symptomatic improvement, with three patients (60%) showing significant improvement and 18 patients (35%) showing mild improvement. One patient had worsening hemoptysis, and two patients (4%) did not return for assessment. Median time to symptomatic relapse after the first fraction of brachytherapy was six months (range, one to more than six months). Complete or partial tumor regression was demonstrated in 44 patients (85%) on repeat bronchoscopy. For the entire cohort, median follow-up was 31 months, and median overall actuarial survival from the first brachytherapy session was seven months (range, 0-55). Fifty patients (96%) tolerated treatment without acute, treatment-related complications. Significant treatment-related complications (Grade 3 or 4) were reported as possibly occurring in two patients (4%): One patient developed a pneumothorax six weeks after brachytherapy, and one patient died from hemoptysis 48 hours after treatment; however, it was unknown whether hemoptysis was due to brachytherapy or to erosion of tumor into a blood vessel.

A 2013 comparative effectiveness review prepared for the Agency for Healthcare Research and Quality reviewed local nonsurgical therapies for symptomatic obstructive NSCLC. For patients with obstruction due to inoperable NSCLC, four RCTs (total N=268) examined endobronchial brachytherapy alone or in combination with external-beam radiation therapy or Nd-YAG laser therapy for palliative or curative intent. All RCTs were determined to be of poor quality. Seven single-arm studies (total N=740) examined endobronchial brachytherapy alone or in combination with external-beam radiation therapy, stent placement, or chemoradiotherapy plus photodynamic therapy for palliative or curative intent. The evidence was considered “insufficient to permit conclusions on the comparative effectiveness of local nonsurgical therapies for…inoperable NSCLC patients with endoluminal tumor causing pulmonary symptoms.”

Endobronchial brachytherapy as primary treatment
Candidates for primary treatment have principally included patients with early stage endobronchial tumors who are not candidates for surgical resection or external beam radiation due to comorbidities or the location of the tumor. Results have predominantly been reported in case series where complete response (CR) rates in the range of 50–80% have been noted.

There have also been early investigations for the use of brachytherapy to deliver a focused radiation boost to patients undergoing curative external beam radiation therapy. External beam radiation therapy is typically the primary treatment for the majority of patients with NSCLC due to the fact that patients usually present with surgically unresectable disease and that NSCLC is unresponsive to chemotherapy.

Aumont-le Guilcher et al reported on 226 patients with primary non-small cell carcinoma (endobronchial only) who underwent high-dose-rate brachytherapy because of contraindications to surgery and external-beam radiation therapy. The patient sample comprised 223 men and three women from nine institutions; mean age was 62 years (range, 40-84). Tumor histology was squamous cell in 96%, adenocarcinoma in 2%, and other in 2%. Response to high-dose-rate brachytherapy at two to three months was classified as complete histologic response (disappearance of the lesion by bronchoscopy and negative biopsy), complete macroscopic response (disappearance of the lesion but no biopsy), partial response (greater than 50% decrease in endobronchial tumor volume), or progression (increase in endobronchial tumor volume or
tumor visible on computed tomography scan). At three months, complete local response was observed in 213 patients (94%), and in 137 patients with biopsies, 126 (91%) had a CR. Seven patients had tumor progression, five had a partial response, and one had stable disease. Overall survival was 57% at two years and 29% at five years. Median survival was 28.6 months. Cancer-specific survival was 81% at two years and 56% at five years. Complications led to treatment interruption in 4.5% of patients. Fatal complications (most commonly fatal hemoptysis) occurred in 6% of patients.

Skowronek et al reported on a small cohort of 34 patients in Poland who had stage IB-III lung cancer (74% squamous cell carcinoma histology; all distant metastasis-free) who had undergone lobar resection. Thirteen patients (38%) developed postoperative recurrence in the bronchial stump, and 21 patients (72%) had histopathologically positive margins after non-radical resection. All patients had dyspnea and cough, and eight patients (24%) had hemoptysis. Median patient age was 57 years (range, 47-73). Median time to recurrence after surgery was 11 months. It was not specified if patients were candidates for reoperation. Nine patients received high-dose-rate endobronchial brachytherapy (total dose, 12 Gy) in combination with external-beam radiation therapy (total dose, 50 Gy), and 25 patients received brachytherapy alone (total dose, 30 Gy). At one month, complete local and radiologic response was observed in 25 patients (74%), with 100% complete remission in the non-radical surgery group. All partial responses occurred in the recurrent tumor group (9 [69%] of 13 patients). Median overall survival for the entire cohort was 19 months. With two years median follow-up, two-year overall survival was 15% in the group with recurrent tumor and 48% in the non-radical resection group (Kaplan-Meier log-rank test, p=0.05). Adverse events were not reported.

Rochet et al reported on a cohort of 35 patients in Germany who had Stage I-III (31% squamous cell carcinoma histology; all distant metastasis-free) inoperable NSCLC and received primary treatment with high-dose-rate endobronchial brachytherapy (median total dose, 15 Gy) in combination with external-beam radiation therapy (median total dose, 50 Gy). Mean age was 64 years (range, 45-75). With 26 months median follow-up, median overall survival was 39 months. One-, two-, and five-year overall survival was 76%, 61%, and 28%, respectively. Median progression-free and local progression-free survival was 17 months and 42 months, respectively. In patients without mediastinal node involvement, five-year local progression-free survival was 56% versus 11% with positive mediastinal nodes (Kaplan-Meier method log-rank test, p=0.008). Grade 3 adverse events were hemoptysis in two patients and necrosis in one patient. Fatal hemoptysis in one patient resulted from tumor recurrence.

Endobronchial brachytherapy in the treatment of hyperplastic granulation tissue
Endobronchial brachytherapy has also been investigated to treat hyperplastic granulation tissue causing recurrent airway stenosis complicating lung transplantation or stent placement. A 2008 case series reported on the use of endobronchial brachytherapy in eight patients following excision of obstructive granulation tissue; six had a good or excellent subjective early response for the first six months. A 2006 case series used endobronchial brachytherapy in five patients with benign granulation tissue following lung transplantation that was refractory to multiple other bronchoscopic interventions. After a median follow-up of 12 months, three of the five patients had marked symptom improvement. While these cases series offer positive outcomes,
larger trials with adequate follow-up are needed to fully evaluate the potential role of endobronchial brachytherapy in the treatment of granulation tissue.

Rahman et al reported long-term follow-up of 115 patients who underwent various flexible bronchoscopic therapeutic modalities for the management of benign tracheal stenosis between 2001 and 2009. High-dose-rate endobronchial brachytherapy was used in cases of refractory stent-related granulation tissue formation, defined as requiring three or more interventions within six months due to recurrent granulation tissue formation. All patients presented with signs and symptoms of upper airway obstruction, including shortness of breath, stridor, cough, dyspnea, and wheezing. Stents were placed in 33 patients to restore airway patency, and 28 of these patients underwent brachytherapy to prevent granulation tissue reformation. All 28 patients experienced a reduction in therapeutic bronchoscopic procedures after brachytherapy compared with the pretreatment period; no further details about response duration or other outcomes were reported. There were no treatment-related complications. Although this case series reported positive results, small sample size and concerns about outcome reporting limit conclusions that can be drawn.

Summary
Many patients with non-small-cell lung cancer are initially treated with external-beam radiation therapy but ultimately experience local recurrence; many are not candidates for further external-beam radiation therapy due to the limited tolerance of normal tissue. If symptoms persist following external-beam radiation, endobronchial brachytherapy is well-accepted as a short-term palliation for such symptoms as hemoptysis, cough, dyspnea, and resolution of obstructive atelectasis or pneumonitis.

Candidates for primary treatment have principally included patients with early-stage endobronchial tumors who are not candidates for surgical resection or external-beam radiation due to comorbidities or the location of the tumor. Results have predominantly been reported in case series for which complete response rates in the range of 50 – 80% have been noted. Comparative trials are needed to determine if survival or quality-of-life outcomes are improved compared with no treatment in these patients.

Endobronchial brachytherapy has also been investigated to treat hyperplastic granulation tissue causing recurrent airway stenosis complicating lung transplantation or stent placement. Case series offer positive outcomes, however, larger trials with adequate follow-up are needed to fully evaluate the potential role of endobronchial brachytherapy in the treatment of granulation tissue.

Practice Guidelines and Position Statements
NCCN guidelines recommend endobronchial brachytherapy for locoregional recurrence of non-small cell carcinoma with endobronchial obstruction or severe hemoptysis (category 2A).

The American College of Radiology (ACR) Appropriateness Criteria
ACR Appropriateness Criteria are developed by expert consensus and literature review. Several publications address radiation and non-surgical treatments of lung cancer.
• For nonsurgical treatment of NSCLC in patients with poor performance status or for palliative intent, the expert panel considered endobronchial brachytherapy “useful for patients with symptomatic endobronchial tumors.”

• For nonsurgical treatment of NSCLC in patients with good performance status or for definitive intent (no distant metastases), the panel considered endobronchial brachytherapy not appropriate, except in combination with external-beam radiation therapy for patients who are symptomatic due to endoluminal obstruction, e.g., postobstructive pneumonia.

• Endobronchial brachytherapy is not included in appropriateness criteria for radiation therapy of small cell lung cancer.

Third International Lung Cancer Consensus Workshop
The Workshop generated consensus statements on palliative radiotherapy and symptom control. For endobronchial brachytherapy, experts concluded that there was no evidence to routinely recommend endobronchial brachytherapy alone or in combination with other palliative maneuvers in the initial palliative management of endobronchial obstruction resulting from lung cancer. However, for palliative management of patients with recurrent endobronchial obstruction after external radiation therapy or to treat a central obstruction before definitive radiation therapy to re-establish airway patency, endobronchial brachytherapy may be a reasonable option.

Key Words:
Brachytherapy, Endobronchial, Endobronchial Brachytherapy, Lung Cancer, Brachytherapy

Approved by Governing Bodies:
Not applicable at this time.

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.
Pre-certification requirements: Not applicable.

Coding:
CPT Codes: 31643 Bronchoscopy (rigid or flexible); with placement of catheter(s) for intracavitary radionuclide application
77326 – 77328 Brachytherapy isodose plan; code range
77761 – 77763 Intracavitary radiation source application; code range
77785 – 77787 Remote afterloading high dose rate radionuclide brachytherapy; code range
References:

Policy History:
Medical Policy Group, April 2011 (1)
Medical Policy Administration Committee, April 2011
Available for comment April 13 – May 30, 2011
Medical Policy Group, June 2012 (3): 2012 Updates to Key Points
Medical Policy Panel, February 2013
Medical Policy Group, February 2013 (3): 2013 Updates to Key Points and References; no change in policy statement
Medical Policy Panel, February 2014
Medical Policy Group, February 2014 (3): 2014 Updates to Key Points & References; no change in policy statement

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.