



# CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

**Subject Proton Beam Therapy for Lung Cancer**

**Effective Date .....6/15/2011**  
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## Hyperlink to Related Coverage Policies

- Intensity-Modulated Radiation Therapy (IMRT)
- Neutron Beam Therapy
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- Radiofrequency Ablation (RFA) of Pulmonary Tumors
- Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT)
- Tumor Markers for Diagnosis and Management of Cancer

### INSTRUCTIONS FOR USE

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## Coverage Policy

**CIGNA does not cover proton beam therapy for the treatment of lung cancer because it is considered experimental, investigational or unproven.**

## General Background

Cancers that develop in the lungs are categorized as small cell lung cancer (SCLC) (e.g., oat cell or small cell undifferentiated carcinoma), or non-small cell lung cancer (NSCLC). NSCLC is more common, less aggressive, and identified by the cell type in which the cancer develops (e.g., squamous cell carcinoma, epidermoid carcinoma, adenocarcinoma, and large cell carcinoma).

The treatment of lung cancer depends on the type of cancer, tumor size, location, and comorbidities. Treatment includes one, or a combination of, surgical excision, chemotherapy, conventional radiation therapy (i.e., photon therapy), intensity modulated radiation therapy (IMRT), stereotactic radiosurgery, and photodynamic therapy. Proton beam therapy (PBT) has been proposed as a treatment option for localized NSCLC in patients who are poor surgical candidates (e.g., due to age and/or comorbidities) or who refuse surgical excision. Preservation of

surrounding, noncancerous tissue is especially important in patients who have underlying pulmonary disease (e.g., chronic obstructive pulmonary disease [COPD]).

Proton beam therapy (PBT) is one form of conformal particle therapy, meaning that a focused dose of radiation energy can be delivered to the targeted area while surrounding normal tissue receives minimal radiation. Conventional external beam radiation therapy (EBRT) delivers radiation to all tissue, diseased and normal, and targeted tissue only receives 60–70% of the intended dose. Because PBT releases its highest percentage of energy at the end of its path (i.e., Bragg peak), 100% dosage is deposited at the diseased tissue. The cyclotrons that deliver proton therapy use specialized computer planning to identify the internal landmarks to be treated with the proton beam (Smith, et al., 2006; MacDonald, et al., 2006; Bjelkengren and Glimelius, 2005; Chen and Girvigian, 2005; Bush, et al., 2004).

Reported toxicities of PBT include: fatigue, fever, dermatitis, esophagitis, leucopenia, anemia, thrombocytopenia, radiation pneumonitis, atelectasis, painful subcutaneous induration, fibrotic changes, pleural effusion and chest wall myositis. Typically, toxicities are short-term and respond well to treatment. One of the disadvantages of the use of PBT for the treatment of lung tumors is that the stopping region of protons in lung tissue is less precise because aerated lung tissue is less dense than soft tissues in other areas of the body, allowing unexpected high doses in normal lung tissue and areas behind the lung (Hata, et al., 2007; Nihei, et al., 2006; Bush, et al., 2004; Shioyama, et al., 2003).

### **U.S. Food and Drug Administration (FDA)**

Proton beam therapy systems are approved by the FDA 510(k) process as a “medical device designed to produce and deliver a proton beam for the treatment of patients with localized tumors and other conditions susceptible to treatment by radiation” (FDA, 2006). Examples of such systems are the Optivus Proton Beam Therapy System (Optivus Technology Inc., Loma Linda, CA) and the Probeat (Hitachi, Ltd., Power Systems Group, Tokyo, Japan) (FDA, 2006; FDA, 2000).

### **Literature Review**

There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and effectiveness of PBT for the treatment of lung cancers. Available published studies are primarily in the form of case series or retrospective reviews with small heterogeneous, patient populations and do not compare PBT to established radiation therapies. Outcomes from PBT studies are difficult to compare due to the variations in the types of equipment, dosage regimens, planning systems used, and outcomes reported. Well-designed, prospective studies are needed to validate the clinical effectiveness of PBT for the treatment of lung cancer.

Pijls-Johannesma et al. (2010) conducted a systematic review to evaluate the clinical and cost effectiveness of particle therapy, including proton beam therapy, for the treatment of NSCLC, primarily stage I. Five PBT studies (n=214) met inclusion criteria and included one phase II study, two prospective studies, and two retrospective studies. The two- to five-year local tumor control rates ranged from 57%–87%. The two- to five-year overall survival rates were 31%–74% and 23%, respectively. The two- to five-year cause-specific survival rates were 58%–86% and 46%, respectively. Side-effects included grades 2 and 3 pneumonitis (5%) and late grades 2 and 3 toxicity (10%).

Grutters et al. (2010) conducted a systematic review and meta-analysis to compare photon and particle (i.e., protons and carbon-ions) therapy for the treatment of NSCLC, primarily stage I. Eleven conventional radiotherapy (CRT) studies, 11 stereotactic radiotherapy (SBRT) studies, and five proton beam studies (i.e., nonrandomized, prospective and retrospective) met inclusion criteria. Based on meta-analysis, the corrected two-year overall survival estimates were 53% for CRT (n=11), 70% for SBRT (n=11), and 61% for PBT (n=4). The corrected pooled two-year overall survival for CRT was statistically significantly lower compared to SBRT ( $p<0.001$ ), but SBRT and PBT were not significantly different. The corrected two-year disease-specific survival estimates were 67% for CRT, 83% for SBRT, and 74% for proton. The pooled two-year disease-specific survival rate for CRT was statistically significantly lower than that for SBRT ( $p=0.006$ ). The difference in two-year disease-specific survival between SBRT and PBT was not significant. The corrected pooled estimates for five-year overall survival were 19% for CRT (n=5), 42% for SBRT (n=5), and 40% for proton therapy (n=2). The corrected pooled 5-year overall survival for CRT was statistically significantly lower than that for SBRT ( $p<0.001$ ) and proton therapy ( $p=0.014$ ). The five-year overall survival was not statistically different between SBRT and PBT. Five-year disease-specific survival for CRT (43%) was statistically significantly lower than that for SBRT (63%;  $p=0.045$ ). The authors cautioned that because of the limited follow-up in SBRT and particle

studies, the five year outcomes should be interpreted with caution. Correcting for the percentage of medically inoperable patients for five-year outcomes, survival rates increased for CRT and fell for PBT and SBRT. Adverse events were infrequent for all treatment modalities for patients with stage I NSCLC, but difficult to compare across therapies due to poor or incongruous reporting. No estimates for advanced NSCLC were derived due to the “poor data.”

A retrospective review was conducted by Nakayama et al. (2010) on patients (n=55) with stage I NSCLC treated with PBT. Seven patients had previously undergone surgical resection and the remaining patients were either medically inoperable or refused surgery. The proton dosage varied based on the location of the tumor. Follow-up ranged from 1.4–53.3 months. Two years following therapy, the overall survival rate was 97.8%, the progression-free survival rate was 88.7%, and the local control rate was 97.0%. The three-year progression free survival rate was 78.9%. Seven patients experienced recurrence. Complications included pulmonary function deterioration, pneumonitis, and rib fracture.

Widesott et al. (2008) conducted a systematic review to assess the role of PBT in the treatment of NSCLC. Thirteen studies, including mainly stage I-II tumors, met inclusion criteria and were available, none of which were prospective trials. Five studies were related to clinical outcomes (n=214), the remaining studies were related to treatment planning or technical/dosimetric considerations. Early-stage disease was present in 181 patients and advanced disease in 33 patients. Median follow-ups ranged from 14–30 months. Two-year local control rates were reported at 80%–95% and overall survival rate of 74%–84%. From two studies, it was noted that PBT could be used for potential dose escalation and/or sparing of surrounding tissue. The studies included small patient populations and methodological weaknesses yielding limited data and inability to draw definitive conclusions on the clinical application of PBT.

In a prospective case series, Hata et al. (2007) reported on 21 patients with stage I NSCLC (N=11 stage IA [T1N0M0]; N=10 stage IB [T2N0M0]) who received hypofractionated PBT. Nine patients were inoperable due to comorbidities, and 11 refused surgery. Cancer types included squamous cell, adenocarcinoma, and large cell carcinoma. Within 10–54 months following irradiation, two patients died of cancer, two died of pneumonia and 17 survived. At two years, the overall survival rate was 74%; the cause-specific survival rate was 86%; local progression-free was 95%; and the disease-free rate was 79%. Within 6–29 months following surgery, five patients experienced recurrence. Acute toxicities (i.e., leucopenia, anemia, thrombocytopenia, dermatitis, radiation pneumonitis) were transient, requiring no treatment and late toxicities (e.g., painful subcutaneous induration and chest wall myositis) subsided with the use of anti-inflammatory agents. All fibrotic changes were asymptomatic.

Nihei et al. (2006) retrospectively reported on 37 patients with stage IA (n=17) or stage IB (n=20) NSCLC who were medically inoperable or who elected PBT instead of surgery. Follow-up ranged from 3–62 months. The two-year overall survival rate was 84%; the local progression-free survival rate was 80%; the locoregional relapse-free survival rate was 79% for stage IA and 60% for stage IB. Acute toxicities included dermatitis, esophagitis, and fever. Late toxicities included chest pain, radiation pneumonitis, and pleural effusion. The late pulmonary toxicities were more prominent in stage IB patients who received a higher proton dosage.

In a phase II prospective study, Bush et al. (2004) treated stage I NSCLC patients (n=68) with PBT. Patients were either medically inoperable or refused surgery. The three-year overall survival rate was 44%, local-control rate was 74%, disease-specific rate was 72%, and the metastatic relapse rate was 31%. A significant difference was noted in the local disease control rate of T1 and T2 tumors (i.e., T1 tumor rate was 87% compared to 49% of T2 tumors). Acute toxicities included mild fatigue and radiation dermatitis. Tumor relapse occurred more often in T2 tumors greater than three centimeters (cm) in size.

To evaluate survival rates and disease-free rates, Shioyama et al. (2003) conducted a case series of patients (n=51) with inoperable NSCLC who were treated with PBT. The types of cancers in the study group included: 28 stage I, nine stage II, eight stage III, one stage IV, five recurrent disease, 33 squamous cell, 17 adenocarcinoma and one large-cell carcinoma. Follow-up ranged from 18–153 months. The five-year in-field local-control rate was 89% for stage IA patients and 39% for stage IB patients. The five-year overall survival rate was 29% for all patients, with the highest percentage occurring in the stage IA group (70%) compared to the stage IB group (16%). The overall five-year cause-specific survival rate was 47%, and the disease-free survival rate was 37%, with the best outcome reported in stage I patients. Toxicities following treatment included lung fibrosis, atelectasis, skin and subcutaneous tissue reactions, and mild esophagitis.

Two earlier prospective studies compared photon/proton therapy with PBT alone. Bush et al. (November 1999) conducted a study of patients (n=37) with stages I-IIIa NSCLC who were medically inoperable or refused surgery. For all patients at two years, the overall survival rate was 31% (39% for stage I and 13% for stage IIIA); the disease-free rate was 63% (86% for stage I and 19% for stage IIIA); and the local tumor control rate was 87%. Patients who received the photon boost developed some increased consolidation and pulmonary damage which was not experienced in the PBT-only group. Bush et al. (March 1999) conducted a prospective study (n=35) to determine the extent of lung injury received from photon/proton therapy compared to PBT alone in patients with stage I-IIIa lung cancer. At six months follow-up, the maximum injury score in the photon/proton group was three in four patients, two in four patients and one in three patients, with no injury occurring in two patients. In the PBT-only group, the maximal injury score was one in four patients and zero in the remaining eight patients.

### **Technology Assessments**

**Agency for Healthcare Research and Quality (AHRQ):** AHRQ (2009) reviewed available studies evaluating particle beam radiation therapies, including proton beam, for the treatment of various types of cancer including non-small cell lung cancer (primarily, stage 1 disease) (n=17 studies). AHRQ reported that the majority of the studies included heterogeneous patient populations, did not use concurrent controls, and employed different definitions for outcomes and harms. Studies comparing particle beam therapy with conventional radiotherapy, intensity-modulated radiotherapy (IMRT), and stereotactic photon therapy are needed. The report concluded that studies on charged particle therapy “do not document the circumstances in contemporary treatment strategies in which radiotherapy with charged particles is superior to other modalities. Comparative studies in general and randomized trials in particular (when feasible) are needed to document the theoretical advantages of charged particle radiotherapy to specific clinical situations.”

**Blue Cross and Blue Shield Association (BCBSA):** In a technology assessment, the BCBSA Technology Evaluation Center (TEC) (2011) evaluated the health outcomes of PBT compared to stereotactic body radiotherapy (SBRT) for the treatment of non-small cell lung cancer. No comparative studies, randomized or nonrandomized controlled trials were found. Eight case series (340) were included in the evaluation. A total of 88.5% of all patients had stage I disease. Seven studies reported a two-year overall survival probably of 39%–98% and five studies reported a 25%–78% probably at five-years. An indirect meta-analysis reported a nonsignificant difference between pooled two-year overall and five-year overall survival estimates favoring SBRT over PBT. The authors concluded that “overall, evidence is insufficient to permit conclusions about the results of PBT for any stage of non-small cell lung cancer.” “Whether PBT for non-small cell lung cancer improves outcomes in any setting has not yet been established.”

**ECRI Institute:** In an Emerging Technology Evidence Report (2011), ECRI institute reported that proposed indications for PBT include non-small cell lung cancer, but it is generally not indicated for nonsolid tumors and tumors that are likely to metastasize, including small-cell lung cancer. ECRI noted that they were unable to identify any technical standards or practice guidelines that specifically addressed PBT and that there were “no appropriately designed studies (i.e., randomized controlled trials, high quality prospective case-controlled studies) that compared the efficacy of proton therapy to other forms of radiation therapy for similar patients.”

### **Professional Societies/Organizations**

**American College of Chest Physicians (ACCP):** The 2007 guidelines of the ACCP discussed the treatment and management of bronchioloalveolar lung cancer (Arenberg, 2007), small cell lung cancer (Samson, et al., 2007; Simon and Turrisi, 2007), non-small cell lung cancer stages I and II (Scott, et al., 2007), stage IIIA (Robinson, et al., 2007), stage IIIB (Jett, et al., 2007), stage IV (Socinski, et al., 2007), and other forms of lung cancer (e.g., Pancoast tumor; NSCLC T4N0,1M0 tumors; satellite lesions) (Shen, et al., 2007). When possible, surgical excision is the “gold standard” treatment for lung cancer. Chemotherapy and/or conventional radiation therapy may be the treatment options of choice for inoperable lung cancers or for patients who refuse surgery. They may also be used as adjunctive therapies following surgical excision. The ACCP does not discuss proton beam therapy as a treatment option for the management of lung cancer.

**American College of Radiology (ACR):** The 2010 ACR Appropriateness Criteria<sup>®</sup> for nonsurgical treatment of non-small cell lung cancer included a discussion on PBT. ACR noted that studies are small single-institution series and the various techniques used by the institutions made it difficult to compare the data as a whole. Technical issues related to PBT include “geometric uncertainty about the range of a given proton beam, and

differences in tissue density between tumors and surrounding normal lung tissue.” According to ACR, large prospective trials are underway that will “hopefully clarify the role of PBT in the treatment of lung cancer.”

**European Organization for Research and Treatment of Cancer (EORTC)/International Society for Geriatric Oncology (SIOG):** The EORTC Elderly Task Force and Lung Cancer Group and the SIOG (Pallis, et al., 2010) conducted a systematic review of the literature (n=58 studies) to identify optimum treatment (e.g., surgical intervention, chemotherapy, radiotherapy, and targeted therapy) for elderly patients with all stages of NSCLC. Their recommendations included: 1) surgery is the standard early-stage disease treatment and adjuvant radiotherapy is not recommended due to the “lack of demonstrated benefit”; 2) standard radiotherapy may be a treatment option when done with a curative intent for elderly patients who are not suitable surgical candidates; 3) even though there is a lack of randomized controlled trials, concurrent chemotherapy and standard radiotherapy may be offered to elderly patients with locally advanced NSCLC. Regarding newer radiation techniques, including particle beam therapy, EORTC states further investigation is needed.

**National Comprehensive Cancer Network® (NCCN®):** In their Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology™, NCCN (2011) states that proton beam therapy may be allowed “under strictly defined protocols.” However, NCCN does not provide criteria for “strictly defined protocols.”

### Summary

There is insufficient evidence in the published peer-reviewed scientific literature to support proton beam therapy for the treatment of lung cancer. Direct comparisons to conventional external beam radiation therapy and other established radiation therapies are lacking. The studies have failed to demonstrate consistent outcomes of proton beam therapy as it relates to local progression, recurrence, cause-specific and overall survival rates. Definitive patient selection criteria for proton beam therapy based on tumor grade and size have not been established.

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## Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

### Experimental/Investigational/Unproven/Not Covered:

CPT* Codes	Description
77520	Proton treatment delivery; simple, without compensation
77522	Proton treatment delivery; simple, with compensation
77523	Proton treatment delivery; intermediate
77525	Proton treatment delivery; complex

ICD-9-CM Diagnosis Codes	Description
162.2-162.9	Malignant neoplasm of bronchus, and lung
197.0	Secondary malignant neoplasm of lung
231.2	Carcinoma in situ of respiratory system, bronchus and lung

\*Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.

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## Policy History

<b>Pre-Merger Organizations</b>	<b>Last Review Date</b>	<b>Policy Number</b>	<b>Title</b>
CIGNA HealthCare	6/15/2008	0477	Proton Beam Therapy for Lung Cancer

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