CIGNA HEALTHCARE COVERAGE POSITION

Revised Date 6/15/2007
Original Effective Date 12/15/2004
Coverage Position Number 0251

Subject **Neutron Beam Therapy**

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INSTRUCTIONS FOR USE

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Coverage Position

CIGNA HealthCare covers neutron beam therapy as medically necessary for the treatment of inoperable, unresectable, or locally advanced malignant tumors of the salivary gland when there is failure, contraindication or intolerance to conventional methods of treatment.

CIGNA HealthCare does not cover neutron beam therapy for any other indication because its use is considered experimental, investigational or unproven.

General Background

Radiation therapy can be delivered either internally or externally. Brachytherapy, also called internal radiation therapy, uses an implantable radiation source that is surgically placed in close proximity to the tumor. External beam radiation is beamed from a source external to the body and delivered using either high-energy rays (e.g., x-rays and gamma rays) or particles (e.g., protons, neutrons, electrons, heavy ions, and pions). High-energy rays, which do not have significant mass or charge, release the most energy when they enter the tissue and lose their power exponentially the farther they travel. In contrast, particulate radiation carries a mass and may carry an electrical charge. Particles that carry a mass and a charge release the highest percentage of their energy at the Bragg peak, the end of their path. As a particle travels through the tissue, its velocity decreases. At a predictable distance from its source, which is defined by its initial energy, a greater proportion of the energy release occurs. There is very little energy released proximally or distally to the Bragg peak. Using sophisticated planning and placement equipment, and by controlling the initial energy, it is possible to direct the Bragg peak for a specific particle beam to

an exact three-dimensional location in the body. Neutron beam therapy (NBT), also called fast neutron therapy, has been proposed as an alternative to photon radiation therapy (XRT), and is also proposed for use in combination with photon therapy (i.e., mixed beam radiation therapy [MBT]) (Rossi, et al., 1998; Thurman, et al., 2001; Eng, et al., 2002).

It is hypothesized that NBT is more effective than photon radiation because the cell damage that occurs during NBT is less dependent on oxygen and less dependent on the cell's position in the cell division cycle. Neutron beams deliver 20–100 times more energy (i.e., high linear energy transfer [LET] radiation) than photon radiation, making it potentially more effective in photon-resistant tumors (Hayes, 2004). Following treatment with high LET radiation, the chances of tumor cells repairing themselves is minimal, compared to tumor cell repair following low LET radiation (i.e., photon radiation). Unlike photon therapy, neutron therapy prevents rebuilding of the deoxyribonucleic acid (DNA) of the tumor, halting the tumor growth. Therefore, NBT is proposed for the treatment of localized, malignant tumors that are unresponsive to other forms of therapy (e.g., chemotherapy, surgery, conventional radiation [i.e., photon and electron radiation] and proton beam therapy). It may also be used in conjunction with chemotherapy and/or surgery to reduce the risk that the cancer will return or to eradicate small amounts of remaining cancer (American Cancer Society [ACS] 2005a; Hayes, Jan 2005, updated 2006). The physical properties of the neutron particles allow for precise dose localization and superior depth dose distribution, allowing the delivery of a higher dose within the path that they travel. This makes NBT more damaging to the more resistant, hypoxic cells. As a result, NBT requires fewer treatments over a shorter length of time (Smith, et al., 2006).

NBT is administered at a treatment facility equipped with a superconducting accelerator (i.e., cyclotron). Treatment planning usually involves computed tomography (CT) to locate the tumor and determine its volume. The patient may then receive NBT alone or in combination with conformal XRT. In both cases, the total dose is administered as a series of lower-dose daily fractions, 4–5 times per week for 5–7 weeks. In the case of MBT, radiation treatment generally alternates between 2–3 days of NBT and 2–3 days of photon radiation per week. Treatment verification with a diagnostic x-ray may be required at each visit. Patients require radiological and clinical surveillance to confirm treatment success and to monitor for possible complications and/or tumor recurrence (Haraf, et al., 1995; Austin-Seymour, et al., 1994; Russell, et al., 1990).

NBT is proposed for the treatment of various forms of cancers including, but not limited to:

- salivary gland tumors
- locally advanced head and neck tumors
- locally advanced prostate cancer
- soft tissue sarcomas
- small-cell lung cancer
- breast cancer

Currently, NBT is available in three dedicated patient treatment facilities in the United States: the University of Washington (UW) Medical Center (Seattle, WA); the Harper-Grace Hospital (Detroit, MI); and the Fermi National Accelerator Laboratory (FNAL) (Batavia, IL) (FNAL, 2004; UW Medicine, 2004).

U.S. Food and Drug Administration (FDA)
The equipment used to deliver neutron beam therapy is approved as a Class II, 510(k) device by the U.S. Food and Drug Administration (FDA). Examples of these devices include the Isocentric Neutron Therapy Systems (The Cyclotron Corp., Berkeley, CA), and the Medcyc Superconduct Isocen Neutron Therapy System (Medcyc Corporation, East Lansing, MI).

Literature Review
One of the difficulties in reviewing the literature is that treatment parameters, including type and dose of radiation, vary between studies, hampering comparison of outcomes across studies. In addition, the relative biologic effectiveness (RBE) of the neutron beam varies considerably, depending on its physical properties; therefore, the results of studies conducted at different centers are difficult to compare. Moreover, NBT has undergone technical changes since the earlier trials, and new technologies allow for

advanced neutron beam shaping and targeting capabilities, thus further complicating comparative analysis of clinical outcomes.

Salivary Gland Cancer: Salivary gland cancer may involve the major (i.e., parotid glands, submandibular glands, and sublingual glands) or the 600–1000 minor salivary glands. Minor salivary glands are located beneath the lining of the lips, tongue, hard and soft palate, and inside the cheeks, nose, sinuses, and larynx. The multiple types of carcinomas that can invade the salivary glands include: mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma, polymorphous low-grade adenocarcinoma, and multiple rare carcinomas (e.g., basal cell adenocarcinoma, clear cell carcinoma, cystadenocarcinoma, sebaceous adenocarcinoma, oncocytic carcinoma, salivary duct carcinoma and mucinous adenocarcinoma). Salivary gland cancers occur in 1.2 per 100,000 people, with a third occurring in people under age 55. They are a rare cancer accounting for 5% of all head and neck cancers. The treatment and outcomes of salivary gland tumors depend upon the stage of the cancer, the location(s) of the cancer, presence or absence of metastases and other patient morbidities. The standard treatment for salivary gland cancer is surgical removal. Chemotherapy may be an effective treatment modality for low-grade tumors. Radiation therapy may be used as an adjuvant to surgery when positive margins are present. Radiation therapy may be the first line of treatment. Fast neutron beam may be the radiation therapy of choice for inoperable, recurrent or unresectable tumors (ACS, 2006; National Cancer Institute [NCI], Nov 2005).

Because of the low incidence of the disease, the heterogeneous patient population, and limited neutron facilities, studies on neutron therapy for these cancers are lacking. The studies often include a patient population with diverse tumors occurring in a variety of primary sites. Douglas et al. (2003) conducted a retrospective review of 279 medical records “to evaluate the efficacy of fast neutron radiotherapy for the treatment of salivary gland neoplasms.” Gross residual disease was seen in 263 patients at the time of treatment; 141 patients had major salivary gland tumors; and 138 had minor salivary gland tumors. The follow-up period ranged from 1–142 months. The six-year actuarial survival rate was 67%. The authors concluded that NBT was an effective treatment for patient with gross residual disease, and that it achieved excellent local-regional control in patients without gross disease. Douglas et al. (2001) also reported on 16 patients treated with neutron therapy for recurrent pleomorphic adenomas of the salivary glands, the most common neoplasm of the salivary gland. The 15-year actuarial survival rate was 85%. From this review, they concluded that “neutron radiotherapy offered both excellent local control rates and survival rates in patients with multiple recurrent pleomorphic adenomas that are not candidates for surgical resection, even in the presence of gross residual disease.”

In 2001, Huber et al. conducted a comparative, retrospective study of patients with advanced adenoid cystic carcinoma of the head and neck who had received radiotherapy (i.e., neutron, photon and mixed beam therapy). The 75 patients were treated between 1983 and 1995. All cancers were inoperable, recurrent, or incompletely resected. Twenty-nine of the patients received neutron therapy, 25 received photon therapy, and 21 received mixed beam therapy (i.e., neutron/proton). On an actuarial basis, there was a significant advantage in local control for patients in the neutron group over the MBT and the proton group. The recurrence rate was lower in the neutron group over the other two groups. There was no significant difference in the survival rate between the three groups. The authors concluded that neutron therapy could be recommend in patients with bad prognosis with gross residual disease, unresectable tumors, or inoperable tumors based upon the patient’s situation, preferences, quality of life issues, and accessibility to a neutron facility.

Douglas et al. (1996) reported on the treatment of 84 patients with adenoid cystic carcinoma of minor salivary glands that were treated with fast neutron beam therapy. All patients had unresectable or gross disease, and 17 had received conventional radiotherapy. The five-year actuarial local-regional tumor control rate was 47% for all patients treated with curative intent. The authors stated that fast NBT should be considered as initial primary treatment for this population and in patients who were high-risk surgical candidates.

In 1993, Laramore et al. conducted a randomized clinical trial to compare the efficacy of fast neutron therapy to conventional therapy (i.e., photon and/or electron). All of the patients (n=32) had inoperable primary or recurrent major or minor salivary gland tumors. Patients were stratified according to surgical status, tumor size and histology. The patients who received neutron therapy demonstrated a significant

improvement in local-regional control rate. Ten-year follow-up data demonstrated statistical improvement, but no difference in morbidity. The authors concluded that “fast neutron radiotherapy appears to be the treatment-of-choice for patients with inoperable primary or recurrent malignant salivary gland tumors” (Laramore et al., 1993b).

Professional Societies/Organizations: In their discussion of adenoid cystic carcinoma (AdCC), the American Society of Clinical Oncology (ASCO) states that NBT shows the greatest benefit in patients with salivary gland tumors and AdCC, which most commonly occurs in the salivary gland. Because the side effects from NBT are more severe than those from conventional radiotherapy, ASCO states that NBT is typically used for inoperable or recurrent disease (ASCO, 2007).

The American Cancer Society’s (ACS) discussion of the treatment of salivary gland cancer states, “Some special types of radiation therapy are useful in treating salivary gland cancer. One type is called fast neutron beam radiation. Some doctors think that this is the best kind of radiation to use in curative treatment of salivary gland cancers” (ACS, 2006).

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology regarding head and neck cancers list photon/electron therapy or neutron therapy as definitive radiation therapy options for locoregional disease, unresectable, or gross residual disease of the salivary gland (NCCN, 2006, updated 2007).

The National Cancer Institute (NCI) states that “fast neutron-beam radiation improves disease-free and overall survival in patients with unresectable tumors or for patients with recurrent neoplasms.” They also state that fast neutron beams have been reported to improve disease-free and overall survival in some types of salivary gland tumors. They further state the following are indications for neutron beam therapy:

- stage I tumors with poor prognosis
- stage II tumors that have spread to lymph nodes
- high-grade tumors that are inoperable, unresectable, or recurrent
- stage III major salivary gland tumors that have spread to local lymph nodes (NCI, Nov 2005)

In November 2003, The Agence d’évaluation des technologies et des modes d’intervention en santé (AETMIS) published a technology brief, “The Efficacy of Neutron Therapy in the Treatment of Malignant Salivary Gland Tumors,” in which they state that neutron beam therapy is “more specifically intended for inoperable and unresectable tumors.” In the case of inoperable or unresectable tumors, NBT is the treatment of choice, especially for unresectable cystic adenoid carcinomas of the main or accessory salivary glands. For advanced stage tumors, treatment is palliative. NBT is also a treatment option following surgical intervention for large-volume residual diseases. AETMIS further states that there is a “paucity of efficacy data on neutron therapy.” There are few studies due to the limited number of facilities available to perform this treatment.

In their discussion regarding treatment of tumors of major salivary glands, The American Head and Neck Society states that NBT may be considered as a treatment option for recurrent or unresectable, local-regional disease of the submandibular and parotid glands.

Summary: The peer-reviewed scientific literature and professional societies support the efficacy of NBT for the treatment of inoperable, unresectable, or locally advanced malignant tumors of the salivary gland. The studies included patients with gross residual disease and/or inoperable, recurrent, incompletely resected tumors. Most had been unsuccessfully treated with conventional therapy prior to treatment with NBT.

Other Head and Neck Carcinomas: Other head and neck cancers include cancers of the oral cavity, paranasal sinuses, nasal cavity, pharynx, larynx, and lymph nodes in the upper part of the neck. Tobacco and alcohol are the number one cause of cancers of the oral cavity, oropharynx, hypopharynx, and larynx, with 85% being linked to tobacco use. The treatment of these cancers depends upon the location, stage of cancer, and the patient’s age and morbidities. Treatment modalities include surgical excision,

radiation therapy, and chemotherapy. These therapies may be used alone or in combination (NCI, Mar 2005).

Maor et al. (1995) conducted a randomized trial to compare the efficacy of fast neutron (n=83) therapy to photon therapy (n=86) in patients with Stage II and IV cancers of the oral cavity, oropharynx, hypopharynx, supraglottic larynx and glottic larynx. The initial response rate with neutron therapy was higher, but local control and survival were not improved. The overall results of the study failed to show a lasting advantage of neutron therapy. The authors concluded that "fast neutron therapy for advanced squamous cell carcinoma of the head and neck can only be recommended for patients in whom the logistic benefit of treatment outweighs the increased risk of late toxicity."

A literature review by Hayes (Jan 2005, updated 2006) reported on three randomized trials; one prospective, nonrandomized comparative study; one prospective randomized; and three retrospective reviews that investigated the safety and efficacy of NBR for head and neck cancers. The studies were published between 1975 and 1999. Some of the studies were updates on earlier studies. The literature did not support the use of neutron therapy for other head and neck cancers.

Summary: The studies in the peer-reviewed literature do not support the safety and efficacy of NBT for the treatment of other head and neck cancers.

Prostate Cancer: Adenocarcinoma of the prostate is the second most frequently diagnosed cancer in men living in the United States. Prostate cancer mainly affects men ages 55 and older, with the median age at diagnosis of 72 years. Patients with a family history of prostate cancer are at higher risk for developing the disease. Early symptoms include: frequent urination; difficulties starting urination or holding back urine; inability to urinate; weak or interrupted flow of urine; painful or burning urination; erectile dysfunction; painful ejaculation; and frequent stiffness or pain in the lower back, hips, or upper thighs. If these symptoms are present, a digital rectal exam (DRE) is performed to detect enlargement or irregularity in the prostate. Urine analysis is used to test for hematuria and/or infections. A blood test measures prostate-specific antigen (PSA), a substance that is elevated in the blood of prostate cancer patients. In addition, prostatic acid phosphatase (PAP) levels, an enzyme produced by the prostate, may also be measured and are frequently elevated in cancer patients. Other examinations include: transrectal ultrasound, intravenous (x-ray) pyelogram, and cystoscopy. If the test results suggest the presence of a tumor, a biopsy is performed to confirm the diagnosis (Yonemoto, et al., 1997; Schulte, et al., 2000).

A number of different modalities, including radiation, surgery, and hormonal, chemical, cryoablative, genetic, and immunological therapies provide treatment options for prostate cancer. Careful watching and waiting is sometimes employed when the mortality risk from other causes exceeds the risk from the malignancy. The most frequently used approaches for cancer localized to the prostate are radical prostatectomy and radiation therapy. In advanced disease with metastatic lesions or in patients who have had a recurrence of disease, hormonal therapy is often used. The prognosis is poor for patients with advanced disease in whom hormonal therapy is unsuccessful, and the treatment is usually palliative (Yonemoto, et al., 1997; National Cancer Institute [NCI], 2004).

The relationship between prostate size and the rate of genitourinary complications was characterized in a retrospective study involving 273 patients with stage T1 or T2 organ-confined adenocarcinoma of the prostate who received MBT consisting of nine or 10 neutron Gray (nGY) NBT and 38–40 Gy XRT (Forman, et al., 1999). The neutron dose was delivered in either a four- or a six-field arrangement. The four-year actuarial risk for developing grade 2 or higher genitourinary complications was lower for patients with prostate size of ≤ 74 cm^3 (19%) than for patients with larger prostates (33%); 11% for patients who were treated with four-field, nonaxial NBT; and 35% for patients who were treated with six-field axial NBT. Multivariate analysis identified prostate size as the only significant risk factor for grade 2 or higher genitourinary complications. African-American men were at no higher risk of developing grade 2 or higher genitourinary complications than were Caucasian men.

In a small study by Raymond et al. (1998) involving 25 patients with recurrent prostate cancer following radical prostatectomy, the overall three-year survival rate was 92%, with a three-year biochemical disease-free survival rate of 36%; low baseline PSA levels correlated with improved survival rate (p=0.003). No severe (Radiation Therapy Oncology Group [RTOG] grade ≥ 3) complications occurred.

In a survey study by Reddy et al. (1997), the effect of MBT on quality of life (QOL) was assessed in patients who had been enrolled in a prospective, uncontrolled phase II study that included men with histologically confirmed adenocarcinoma of the prostate (T1N0M0 or T2N0M0) and a total Gleason score of less than or equal to seven. The survey was sent to 83 patients, 90% of whom responded, resulting in a sample size of 75 patients. The results of this study were compared to data published in the peer-reviewed medical literature for QOL following XRT (n=98) and radical prostatectomy (n=757). Patients received a neutron dose of 9–10 nGy and a 38 Gy dose of photon irradiation. In this study, 91% of MBT patients were very satisfied with the treatment; 7% had mixed feelings; and 3% were not satisfied. Most of the patients (84%) were healthy enough to carry out normal activities; the same proportion experienced little or no physical discomfort. The rates of incontinence, pad use, incontinence surgery, and urethral strictures for patients who received MBT (23%, 3%, 0%, and 1%, respectively) were similar to those for patients who received XRT (26%, 11%, 1%, and 5%, respectively), but lower than for patients who underwent surgery (47%, 31%, 6%, and 20%, respectively). In addition, more patients who were treated with MBT (34%) retained potency than did those who received XRT (16%) or underwent surgery (11%). The main complications of MBT were incontinence (33.3%), diarrhea (25%), severe diarrhea (7%), hematochezia (20%), severe hematochezia (3%), and rectal pain (12%). These rates were similar to those reported for XRT and radical prostatectomy (Reddy, et al., 1997). The use of patient self-assessed outcomes, lack of concurrent control or comparative groups, and lack of statistical analysis were the main limitations of this study.

The effect of NBT on potency was investigated in a prospective phase II clinical trial (Hart, et al., 1996) and in the survey study described above (Reddy, et al., 1997). The phase II study included 75 evaluable patients with histologically confirmed early stage adenocarcinoma of the prostate (tumor [T] 1 node [N] 0 metastasis [M] 0 or T2N0M0; total Gleason score less than or equal to seven). Patients received 9–10 nGy NBT to the prostate and seminal vesicles and 38 Gy XRT to the pelvis. At the beginning of the study, 52 of the 75 patients (70%) were potent; of these, 38 (73%) had functional erections, and 14 (27%) had nonfunctional erections. At the end of the study, 35 of 52 patients (67%) retained potency. Overall, 67% of patients did not experience a change in potency. Of the 38 patients with functional erections and the 14 patients with nonfunctional erections, 29 (76%) and six (43%), respectively, maintained their level of potency. The use of adjuvant hormone therapy was not associated with an increased rate of change in erectile function.

Chuba et al. (1996) in a retrospective study investigated the effect of five MBT treatment protocols using NBT doses of 9–20 nGy in 132 patients. The incidence and severity of hip stiffness was NBT dose-dependent; only patients who received at least 15 nGy experienced RTOG grade 3 or higher hip stiffness. Hip stiffness was more common in patients who received large-field radiation therapy (51%) than in patients who underwent small-field treatment (20%; $p<0.001$) (Chuba, et al., 1996). In a retrospective, dose-comparative study involving 132 patients, hip stiffness was associated with marked musculoskeletal changes (Soulen, et al., 1997). In this study, 30% of these patients developed hip complaints; bone/joint abnormalities and muscle and subcutaneous changes occurred in all 25 symptomatic patients. The presence and severity of symptoms was significantly dose-related ($p=0.02$). Russell et al. (1990) reported that, in addition to hip stiffness, NBT and MBT were associated with a higher incidence of neurological complications than XRT was, but the difference was not statistically significant.

Haraf et al. (1995) reported five-year actuarial survival rates of 72% for stage C and 60% for stage D1 patients; 51% of patients developed recurrence or metastasis. The incidence of severe late complications, defined as RTOG grade ≥ 3, was 52%.

The first prospective, nonrandomized dose-finding study involved 136 patients with locally advanced prostate carcinoma not amenable to surgery and without distant metastasis (Cohen, et al., 1995). Patients received three different NBT dose ranges: low (18.0–19.9 nGy; n=5), medium (20.0–20.9 nGy; n=58) and high (21.0–22.9 nGy; n=73). The three-year local control rates were similar for the three groups (80%, 84%, and 82%, respectively), but complication rates were dose-dependent and were higher for patients in the high-dose group (0%, 5.6%, and 12.3%, respectively). The sample size for the low-dose group was very small, however, including only five patients, and no statistical comparison of these outcomes was performed. Therefore, the results do not permit definitive conclusions. The second report described outcomes of three prospective dose-finding studies that evaluated two different doses of MBT

for adenocarcinoma of the prostate. These studies documented a higher incidence of complication rates for high-dose (15 nGy + 18 Gy) MBT than for low-dose (10 nGy + 38 Gy) MBT, but the difference was statistically insignificant. At 20 months, actuarial rates of grade 2 morbidity were 29% for high-dose MBT and 6% for low-dose MBT (p=0.07, not significant). Significantly more patients who received low-dose NBT experienced grade 2 hip stiffness (42%) than did patients in the low-dose MBT group (20%; p=0.01) (Forman, et al., 1996a; Forman, et al., 1996b).

In a retrospective review, Austin-Seymore et al. (1994) investigated the impact on NBT-related mortality when multileaf collimators were used to improve beam shaping. After reviewing the charts of 245 patients, the authors found that patients treated with multileaf collimators experienced significantly fewer complications (10%) than did patients who received NBT in a facility with limited beam-shaping capabilities (39%) (p=0.00007).

In a 1994 randomized study, Russell et al. (1994) compared NBT to XRT in 178 patients with locally advanced prostate cancer, including patients with tumor stage 3–4, N0-1, and M0 tumors of any histological grade, and patients with high-grade T2 tumors. In this study, the five-year actuarial rate of clinical locoregional failure was significantly better for NBT (11%) than for XRT (32%) (p=0.01), but five-year actuarial survival (NBT, 68%; XRT, 73%) and development of distant metastases (NBT, 32%; XRT, 33%) rates were similar for both groups. The therapeutic gain for NBT was offset by the increase in overall late complications observed in NBT patients (NBT, 95%; XRT, 62%; p=0.00007).

The first randomized comparative trial (Laramore, et al., 1985; Russell, et al., 1987; Krieger, et al., 1989; Laramore, et al., 1993b) involved 95 patients under age 80 with stage C or D1 (i.e., Mostofi schema) adenocarcinoma of the prostate. The trial excluded patients who had prior irradiation or extensive surgery of the pelvis and patients with a history of cancer, with the exception of nonmelanoma skin cancer. Patients received either XRT or MBT. In this study, 10-year survival rates were significantly increased for those who received MBT (46%) compared to XRT (29%) (p=0.04). Furthermore, 10-year local control rates were also improved for MBT (70%) compared to XRT (58%) patients (p=0.03). The incidence of development of distant metastases was similar in both groups (MBT, 49%; XRT, 55%). While the overall complication rates were similar for patients in both groups (MBT, 76%; XRT, 64%), MBT patients experienced a higher rate of local edema (MBT, 25%; XRT, 8%), skin complications (MBT, 44%; XRT, 14%), rectal complications (MBT, 58%; XRT, 33%), and overall gastrointestinal complications (MBT, 40%; XRT, 28%).

The National Cancer Institute is currently conducting a trial (n=300) regarding the use of radiation therapy in the treatment of patients with Stage I, Stage II, and Stage III prostate cancer. According to the NCI, the study is being conducted because “it is not yet known which type of radiation therapy is more effective in treating prostate cancer.” The trial will compare the efficacy of neutron and photon radiotherapy to hypofractionated intensity-modulated radiation (NCI, Dec 2005b, updated 2007).

Summary: The peer-reviewed literature does not support the safety and efficacy of NBT for the treatment of prostate cancer.

Soft Tissue Sarcomas: Soft tissue sarcomas are malignant tumors that arise from the mesodermal tissues of the extremities, trunk, retroperitoneal, and head and neck areas. Soft tissue sarcomas most often occur in patients with conditions such as von Recklinghausen’s disease, Gardner’s syndrome, Werner’s syndrome, and Tuberous sclerosis. Prognosis depends upon the patient’s age and histologic grade and stage of the tumor. Treatment also depends upon the tumor characteristics. Surgical incision may completely obliterate a low-grade tumor. Higher grade tumors require more extensive, reconstructive surgery, often in combination with radiation with or without chemotherapy (NCI, 2006; Huber, et. al, 2006).

In 2003, Strander et al. reported on a synthesis of the literature conducted by The Swedish Council of Technology Assessment in Health Care (SBU) on radiation therapy for soft tissue sarcoma (STS). The review included five randomized trials, six prospective studies, 25 retrospective studies, and three additional articles, representing a total of 4579 patients. Two of the studies reported on the outcomes of NBT for the treatment of low- and intermediate-grade soft tissue sarcomas. One study included 61 patients treated with neutron (n=46) or mixed beam photon/neutron (n=15) (Prott et al., 1999), and the

second study compared photon (n=100) to neutron (n=61) therapy (Schonekaes et al., 1999). Based upon this review, the authors concluded that NBT "might be beneficial for patients with low- and intermediate-grade tumors considered inoperable and for those operated with intralesional margins. More severe side effects for neutrons have been registered."

Schwartz et al. (2001) reported on a retrospective analysis of 89 soft tissue sarcoma lesions treated in 72 patients with neutron therapy between 1984 and 1996. NBT alone (73%) and MBT (photon/neutron) were administered. Median follow-up was six months in the palliative group and 38 months in the curative group. The palliative group demonstrated a 62% local relapse-free survival rate and 78% effective clinical response rate. The curative group demonstrated a 59% distant disease-free survival, 68% cause-specific survival, and an overall survival rate of 66% at four years. According to this study, NBT is locally effective for soft tissue and cartilaginous sarcomas having well-recognized high-risk features. Results for palliative patients appeared encouraging. NBT provided "significant symptomatic response for gross disease, with minimal serious chronic sequelae." The authors concluded that "fast neutron radiotherapy should be considered in patients at high risk for local recurrence in both the curative and palliative settings."

Hayes (Jan 2005, updated 2006) included a retrospective review of the treatment of soft tissue sarcoma with NBT vs. XRT in 161 patients. In summary, the five-year survival rate was similar between the groups; the NBT group developed more complications; grades 1 and 2 complication rates were higher in the XRT group, but grades 3 and 4 complication rates were higher in the NBT group.

Professional Societies/Organizations: Based upon the Schwartz et al. (2001) study, the NCI lists fast neutron therapy as one of several standard treatment options for Stage I adult soft tissue sarcomas of the retroperitoneum, trunk, and head and neck (NCI, Apr 2006, updated 2007).

Summary: Due to the limited number of clinical trials, small patient populations and lack of comparative studies to other radiotherapy, the peer-reviewed literature does not support the safety and efficacy of NBT for the treatment of soft tissue sarcomas.

Other Cancers: The peer reviewed literature includes studies that have also considered NBT for the treatment of gynecological cancers, esophageal cancers, breast cancer, bladder cancer, and non-small cell lung cancer. The literature does not support the safety and efficacy of NBT for any of these cancers. There is ongoing controversy regarding the safety and effectiveness of NBT. Advocates propose that it is a more efficient treatment than other alternatives, but based upon small sample sizes, high complication rates, contrasting outcomes when compared with historical data, and high cost and limited availability of neutron facilities, critics do not support its therapeutic value. NBT is used selectively in tumors in which there is some evidence of effectiveness. The increased late toxicity and dose distribution are far less optimal than those of charged particles such as protons; interest in neutron therapy is waning (Smith, et al., 2006; Bell, et al., 2005; Hayes, Jan 2005, updated 2006; Cohen, et al., 1995).

A guideline on the treatment of N2 non-small cell carcinoma (i.e., cancer that has spread to one or more lymph nodes with a tumor size of 3–6 centimeters) by the American College of Radiology (ACR), states that NBT in comparison to photon beam therapy demonstrates "no clear-cut advantage" for the treatment of these patients and, in fact, NBT outcomes were worse than photon beam therapy outcomes (Gopal, et al., 2006).

Summary
Neutron beam therapy (NBT) is an external form of radiation therapy that has been proposed for the treatment of various types of cancer (e.g., salivary gland, head and neck, prostate and soft tissue sarcomas). NBT is proposed to be more effective than other forms of radiation therapy because of its ability to deliver a higher energy level which causes irreversible destruction to tumor cells. There are only three neutron facilities in the United States, which has led to a limited number of scientific studies, and difficulty in comparing outcomes due to the variation in the delivery of NBT.

The peer-reviewed literature supports the use of NBT in the treatment of inoperable, unresectable, or locally advanced malignant tumors of the salivary gland. The safety and efficacy of the use of NBT for the treatment of other forms of cancer has not been proven.

Coding/Billing Information

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

Covered when medically necessary:

CPT®* Codes	Description
77422	High energy neutron radiation treatment delivery; single treatment area using a single port or parallel-opposed ports with no blocks or simple blocking
77423	High energy neutron radiation treatment delivery; 1 or more isocenter(s) with coplanar or non-coplanar geometry with blocking and/or wedge, and/or compensator(s)

HCPCS Codes	Description
	No specific codes

ICD-9-CM Diagnosis Codes	Description
141.0 – 141.9†	Malignant neoplasm of tongue
142.0-142.9	Malignant neoplasms of the salivary glands
145.0†	Malignant neoplasm of cheek mucosa
145.3†	Malignant neoplasm of soft palate
145.9†	Malignant neoplasm of mouth, unspecified site
146.0†	Malignant neoplasm of tonsil

†**Note:** Covered when medically necessary specifically for malignant neoplasms of the salivary glands

Experimental/Investigational/Unproven/Not Covered:

ICD-9-CM Diagnosis Codes	Description
	Multiple/varied

References

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