



CIGNA MEDICAL COVERAGE POLICY

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Subject Hyperthermia Treatment For Cancer

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Coverage Policy

CIGNA covers local external superficial hyperthermia as medically necessary when used in combination with radiation therapy for the treatment of locally advanced or recurrent breast cancer when there is failure, intolerance or contraindication to conventional therapy.

CIGNA does not cover local external superficial hyperthermia for the treatment of any other cancer because it is considered experimental, investigational or unproven.

CIGNA does not cover ANY of the following forms of hyperthermia for the treatment of cancer because each is considered experimental, investigational or unproven:

- local interstitial hyperthermia
- local endocavitary hyperthermia
- regional deep hyperthermia
- whole body hyperthermia (WBH)

General Background

Hyperthermia is a type of cancer treatment in which body tissue is exposed to high temperatures, using external and internal heating devices. Hyperthermia is almost always used with other forms of cancer therapy such as radiation and/or chemotherapy. Research has shown that high temperatures can damage and kill cancer cells, usually with minimal injury to normal tissues. It is proposed that by killing cancer cells and damaging proteins and structures within the cells, hyperthermia may shrink tumors making the cells more sensitive to radiation therapy and/or chemotherapy (American Cancer Society [ACS], 2009; National Cancer Institute [NCI], 2004).

The concept of using heat to treat cancer has been around for a long time, but early attempts to treat cancer with heat had mixed results. Several phase III clinical trials were developed in the 1980s. Given the difficulties with hyperthermia delivery with the available technology and lack of widely applicable quality assurance guidelines enthusiasm for hyperthermia waned in the late 1980s. Despite the challenges with hyperthermia delivery, research continued in the early 1990s (Hurwitz, 2010).

There are several methods of hyperthermia under study including local, regional and whole-body hyperthermia using various strategies to deliver energy or heat. The clinical trials have studied hyperthermia in combination with standard treatment including radiation therapy and/or chemotherapy focusing on the treatment of many types of cancer (e.g., sarcoma, melanoma, head and neck, thyroid, lung, esophagus, breast, kidney, bladder, rectum, liver, appendix, stomach, pancreas, endometrial, ovarian, prostate, cervix, and peritoneal lining). Hyperthermia is generally not used as a stand-alone therapy (ACS, 2009; NCI, 2004). Since adequate heating of the whole tumor volume is difficult except for superficially located small tumors, and in general the reported response duration is short, the use of hyperthermia alone is not recommended (van der Zee, et al., 2008).

Hyperthermia is most effective when the area being treated is kept within an exact temperature range for a defined period of time without affecting nearby tissues. This is challenging since not all body tissues respond in the same way to heat. Small thermometers on the ends of probes are placed in the treatment areas to monitor the desired temperature. Magnetic resonance imaging (MRI) is proposed as a replacement of the probes to monitor the temperature (ACS, 2009).

The possible side effects of hyperthermia depend of the technique being used and the part of the body being treated. Reported adverse events associated with hyperthermia treatment include burns, blisters, and pain. Experience, better skills and improved technology in using hyperthermia treatment have resulted in fewer side effects (ACS, 2009; ECRI, 2007).

The application of hyperthermia is labor-intensive and requires specifically trained staff. The average treatment is one hour for ten sessions although the treatment protocols vary. The tumor sites where hyperthermia can be adequately applied are limited. The number of institutions where hyperthermia treatment is available is limited. Since the number of indications for the use of hyperthermia is limited, institutes are reluctant to invest in equipment and staff (van der Zee, et al., 2008).

Local Hyperthermia: In local hyperthermia, heat is applied to a small area such as a tumor. Various types of energy may be used including microwave, radiofrequency and ultrasound. When ultrasound is used, the technique is called high intensity focused ultrasound, please refer to the CIGNA Coverage Policy, Transrectal Ultrasound (TRUS). There are several approaches to local hyperthermia including (ACS, 2009; NCI, 2004):

- External/Superficial-used to treat tumors just below the skin with placement of external applicators to deliver energy (e.g., skin cancers and skin metastases).
- Intraluminal or endocavitary-used to treat tumors within or near body cavities (e.g., rectum and esophagus) with placement of probes inside the cavity to deliver energy.
- Interstitial-used to treat tumors deep within the body (e.g., brain tumors) with the use of anesthesia to place probes or needles into the tumor to deliver energy.

Regional Hyperthermia: In regional hyperthermia, a part of the body, such as a limb, organ, or body cavity is heated. It is usually combined with chemotherapy or radiation therapy (ACS, 2009).

- Deep tissue-used to treat cancers within the body (e.g., cervical and bladder cancer). External applicators using microwave or radiofrequency energy are positioned around the body cavity or organ to be treated.

- Regional perfusion-used to treat cancers in the arms and legs (e.g., melanoma) or cancers in some organs (e.g., liver and lung). Some of the patient's blood is removed, heated, and then pumped or perfused back into the limb or organ. Anticancer drugs are usually administered during this treatment.
- Hyperthermic intraperitoneal chemotherapy (HIPEC), also referred to as intraperitoneal hyperthermic chemotherapy (IPHC), has been proposed as an alternative for the treatment of cancers within the peritoneal cavity, including primary peritoneal mesothelioma and gastric cancer. The HIPEC is applied during surgery, via an open or closed abdominal approach. The heated chemolytic agent is infused into the peritoneal cavity, raising the temperature of the tissues within the cavity to 106–108 °Fahrenheit (F). For information on the coverage of hyperthermic peritoneal perfusion, please refer to the CIGNA Coverage Policy, Hyperthermic Intraperitoneal Chemotherapy (HIPEC).

The BSD 2000 system (BSD Medical Corporation, Salt Lake City, UT) is cited by many of the regional hyperthermia studies as the device used to administer regional deep hyperthermia. According to the manufacturer website, the BSD-2000 system has not yet received Premarket Approval (PMA) from the U.S. Food and Drug Administration (FDA) for commercial marketing in the United States, but the BSD-2000 has obtained an investigational device exemption (IDE) for placement in the United States for research purposes only.

Whole Body Hyperthermia (WBH): WBH, achieved with either radiant heat or extracorporeal technologies, elevates the temperature of the entire body to at least 41 °C. In radiant WBH, heat is externally applied to the whole body using hot water blankets, hot wax, inductive coils, or thermal chambers. The patient is sedated throughout the WBH procedure, which lasts approximately four hours. The patient reaches target temperature within approximately 1.3 hours, is maintained at 41.8 °C for one hour, and experiences a one-hour cooling phase. During treatment, the esophageal, rectal, skin and ambient air temperatures are monitored at 10-minute intervals. Small probes may be inserted into the tumor under a local anesthetic to monitor the temperature of the affected tissue and surrounding tissue. Heart rate, respiratory rate, and cardiac rhythm are continuously monitored. Patients are returned to regular inpatient rooms after hyperthermia and discharged after 20–24 hours of observation (Robins, et al., 1997; Green, 1991).

Extracorporeal WBH is achieved by reinfusion of extracorporeally heated blood. A circuit of blood is created outside the body by accessing an artery, usually the femoral artery, and creating an extracorporeal loop. The circulating blood is passed through a heating device, usually a water bath or hot air, and the heated blood is then reinjected into a major vein. The desired body temperature is adjusted and controlled by changing the volume flow of the warmed reinfused blood (Wiedemann, et al., 1994).

Extracorporeal hyperthermia treatments are conducted under general anesthesia. To counteract the activation of coagulation by the hemodialyzer, high-dose heparin is administered. An extracorporeal WBH treatment session typically lasts four hours. Target temperature is reached in two hours and is maintained for one hour, followed by a cooling period of one hour. Subsequently, the patient is infused with normal saline to maintain systolic blood pressure above 100 mm Hg. The patient is then monitored weekly for complications (Kerner, et al., 2002; Wiedemann, et al., 1994).

U.S. Food and Drug Administration (FDA)

The FDA has given Premarket Approval (PMA) to hyperthermia systems as Class III devices (FDA, 2010). One device is the BSD-500 Hyperthermia System (BSD Medical Corporation, Salt Lake City, UT) which received PMA in 2004. The BSD-500 is classified as radiofrequency/microwave hyperthermia system for cancer treatment. The PMA approval order statement states that the, BSD-500 hyperthermia system is indicated for treatment of solid malignant tumors by localized heat delivery (FDA, 2004).

Literature Review Local External Superficial Hyperthermia

Breast Cancer: There is limited evidence from randomized controlled or comparative clinical trials (n=81–306) in the peer-reviewed literature to support the safety and efficacy of local external superficial hyperthermia when used in combination with radiation therapy for treatment of locally advanced and recurrent breast cancer for the treatment of patients who have failure, intolerance or contraindication to conventional therapy. The overall body of evidence suggests that local external superficial hyperthermia, when used as part of a multimodal regimen, may aid in increasing local tumor response and greater duration of local control. This does not consistently translate into increased survival rates (Vernon, et al., 1996; Jones, et al., 2005; Wahl, et al, 2008).

Head and Neck, Melanoma, Miscellaneous: Evidence in the peer-reviewed literature on the safety and efficacy of local external superficial hyperthermia as an adjunct treatment for various other primary or metastatic superficial cancers (e.g., superficial recurrent melanoma, cervical lymph node metastases from head and neck cancer) have failed to provide guidance for patient selection, protocols or timing regimens that could be standardized and safely applied. The effectiveness of local external superficial hyperthermia for these uses has not been shown to consistently improve short- or long-term patient treatment outcomes and survival rates in comparison to standard adjuvant radiation therapy.

In a multicenter randomized Phase III clinical trial (n=245), Perez et al. (1991) compared radiation alone to radiation and superficial or external hyperthermia with a 915 megahertz (MHz) microwave applicator in various superficial measurable tumors; head and neck, breast or chest wall, trunk and pelvis, and extremities. Major endpoints included initial tumor response of the treated lesion, its continuous control and treatment delivery. Initial tumor response was defined as complete disappearance of the tumor at the treated site. The overall complete response was not statistically significant (p=0.12). The complete response for radiation alone was 30%. The complete response for radiation and hyperthermia was 32% which was not statistically significant. In lesions < 3 cm treated with radiation and heat, there was improved local control. In lesions > 3 cm, there was no difference in local control between the two treatment arms. At 12 months the probability of remaining in response was the same in both arms. The acute and long-term side effects were the same in both arms.

In a multicenter randomized Phase III clinical trial (n=68 [128 lesions]), Overgaard et al., (1995) compared hyperthermia as an adjunct to radiation of recurrent or metastatic malignant melanoma. Patients had no previous radiation. Hyperthermia was applied externally with microwave or radiofrequency equipment. There were no limitations to the equipment used except that it should be likely to provide a tumor temperature of 43°C. Compliance and tolerance to hyperthermia was good, but the quality of the heating was poor, and most tumors did not receive the prescribed heat dose. The primary endpoint was complete response at three months. Complete response for radiation alone was 35%. The complete response rate for radiation and hyperthermia was 62% (p<0.05). Two year local control for radiation was 46% and for radiation and hyperthermia 28% (p<0.05). The overall 5-year survival rate of the patients was 19%. The hyperthermia was in general well-accepted. In 73% of the treatments, no pain or discomfort was noted. Slight pain was observed in 13% of the heat sessions, moderate pain in 8%, and only in 6% of the treatments the pain was so severe that the treatment was interrupted or stopped. This study is limited by small sample size.

Literature Review Local Interstitial or Endocavitary Hyperthermia

Evidence in the peer-reviewed literature on the safety and efficacy of local interstitial or endocavitary hyperthermia as an adjunctive treatment for various types of cancer (e.g., pelvis, head and neck, breast, melanoma, glioblastoma, rectal) have failed to provide guidance for patient selection, protocols or timing regimens that could be standardized and safely applied. The body of evidence does not consistently translate that local interstitial or endocavitary hyperthermia, when used as part of a multimodal regimen, may aid in tumor and clinical response for various cancers. The duration of follow-up varied from several months to several years. The results do not consistently translate into increased survival rates.

Head, Neck, Pelvis, Breast, Melanoma, Others: In a randomized controlled trial, Emami et al. (1996) studied if interstitial thermoradiotherapy (ITRT) improves tumor regression/control in accessible lesions in comparison with interstitial radiotherapy (IRT) alone and to assess the skin and soft tissue complications with either modality. One hundred seventy-three cases were analyzed (87 patients in the IRT group and 86 in the ITRT arm). The two arms were well balanced regarding stratification criteria. Most tumors were in the head and neck (40% in the IRT group and 46% in the ITRT group,) and pelvis (42% and 43%, respectively). For the IRT alone group the CR was 53% with two year overall survival of 34%. For the ITRT group the complete response was 55% with two year overall survival 35%. The results are not statistically significant. The authors reported that “interstitial hyperthermia, as applied in this randomized study, did not show any additional beneficial effects over interstitial radiotherapy alone. Delivery of hyperthermia remains a major obstacle (since only one patient met the basic minimum adequacy criteria as defined in this study). The benefit of hyperthermia in addition to radiation therapy still remains to be proven in properly randomized prospective clinical trials after substantial technical improvements in heat delivery and dosimetry are achieved.”

Glioblastoma: In a randomized controlled trial, Sneed et al. (1998) investigated if adjuvant interstitial hyperthermia significantly improves survival of patients with glioblastoma undergoing brachytherapy boost after

conventional radiotherapy. Adults with newly-diagnosed, focal, supratentorial glioblastoma ≤ 5 cm in diameter were treated postoperatively with partial brain radiotherapy. Those patients whose tumor was still implantable after teletherapy were randomized to brachytherapy boost \pm heat therapy for 30 min immediately before and after brachytherapy. Time to progression (TTP) and survival from date of diagnosis were estimated using the Kaplan-Meier method. A total of 112 eligible patients were entered in the trial. Due mainly to tumor progression or patient refusal, 33 patients were never randomized. Of the patients, 39 were randomized to brachytherapy and 40 to brachytherapy plus hyperthermia. Of the patients, 39 were randomized to brachytherapy and 40 to brachytherapy + hyperthermia (HT). For the 33 no heat patients and 35 heat patients who underwent brachytherapy boost, TTP and survival were significantly longer for heat than no heat ($p=0.045$ and $p=0.02$, respectively; median survival 85 weeks versus 76 weeks; 2-year survival 31% versus 15%). Improved survival was associated with randomization to heat ($p=0.008$; hazard ratio 0.51). There were no Grade 5 toxicities, 2 Grade 4 toxicities (1 on each arm), and 7 Grade 3 toxicities (1 on no heat and 6 on the heat arm). The reoperation rates for tumor and/or necrosis was 58% for the no heat arm and 69% for heat arm. This study is limited by small sample size.

Literature Review Regional Deep Hyperthermia

Evidence in the peer-reviewed literature on the safety and efficacy of regional deep hyperthermia as an adjunctive treatment for various types of cancer (e.g., cervical, lung, soft tissue sarcoma) have failed to provide guidance for patient selection, protocols or timing regimens that could be standardized and safely applied. The body of evidence does not consistently translate that regional deep hyperthermia, when used as part of a multimodal regimen, may aid in tumor and clinical response for various cancers. The duration of follow-up varied from several months to several years. The results do not consistently translate into increased survival rates.

Cervical Cancer: In a multicenter Phase I/II prospective feasibility study, Westermann et al. (2005) studied the efficacy of the combination of hyperthermia, radiotherapy and cisplatin modalities in previously untreated patients with cervical carcinoma. Patients with advanced cervical carcinoma were registered prospectively in the U.S., Norway, and the Netherlands. Sixty-eight patients with a median age of 45 years were enrolled. Sixty-two patients had squamous cell histology, 42 patients had FIGO Stage IIB disease, and 21 patients had Stage IIIB disease. The endpoint was the number of patients who were able to complete treatment, defined as full-dose radiotherapy, at least four cisplatin courses, and at least four hyperthermia courses. Acceptable was defined as $\geq 90\%$ patients receiving full treatment, and unacceptable was defined as $< 70\%$ of patients receiving planned treatment. External-beam radiotherapy and brachytherapy were administered for a biologically effective dose ≥ 6.7 gray. At least four courses of weekly cisplatin and four sessions of weekly locoregional hyperthermia were added to radiotherapy. Five treatments were planned using a BSD 2000 annular phased array (BSD Medical Corp, Salt Lake City, UT) or the 4-waveguide applicator system (Amsterdam only). Thermometry catheters were placed in the rectum, bladder, and cervical os, vagina, or intratumoral space (Bergen) for thermal dose calculations. Power output was increased until the patient's tolerance threshold was reached, following appropriate adjustments of treatment settings. The objective of hyperthermia treatment was to continue treatment for 60 minutes after cervical os or vaginal measurements reached 40°C (Norway, U.S.) or 41°C (The Netherlands) or, if that temperature was not reached within 30 minutes, for a maximum of 90 minutes. Full-dose radiotherapy was delivered to all patients according to plan. At least four courses of chemotherapy were received by 97% of patients, and at least four courses of hyperthermia treatment were received by 93% of patients. Toxicity was fully comparable to that described for chemoradiotherapy alone, and the median total treatment time was 45 days. Sixty-one of 68 patients achieved clinical complete remission with trimodality treatment, for a complete remission rate of 90%. There was no significant difference in response rates between the countries. After a median follow-up of 538 days, 2 patients were lost to follow-up. Of the remaining 66 patients, 11 died of disease, and 55 remained alive, including 6 patients with recurrent disease. The disease-free survival rate at 2 years (from the day of registration in the study) was 71.6% (95%CI, 55.1-82.8%), and the overall survival rate at 2 years was 78.5% (95%CI, 63.9-90.0%). Specific hyperthermia-related side effects consisted of pain ($n=5$), Grade 1 burns ($n=12$), and subcutaneous fatty necrosis (Grade 1-2; $n=5$). The authors reported that "Based on this study, an international, randomized, Phase III trial of chemoradiotherapy with or without hyperthermia has been launched. The study will randomize 400 patients so that it is powered to detect a 15% improvement in 5-year failure-free survival (i.e., from 50% to 65%) and overall survival (i.e., from 60% to 75%)." This study lacked a comparison group.

In a multicenter prospective randomized trial, Vasanthan et al. (2005) investigated radiotherapy in combination with regional hyperthermia to clarify whether the combination improves the rate of local control, compared with radiotherapy alone. A total of 110 patients with biopsy-proven, locally advanced carcinoma of the uterine cervix

were randomized to treatment by radiotherapy with or without hyperthermia. The patients were stratified by institution, stage, and histologic type. Each patient received external beam radiation therapy and brachytherapy. For the patients randomized to receive hyperthermia, a minimum of five sessions (60 min each, once per week) were administered, employing a radiofrequency capacitive heating device. The median follow-up period was 466 days for all the patients and 512 days for the surviving patients. The authors reported that this study failed to show any benefit from the addition of hyperthermia to radiotherapy in the treatment of locally advanced carcinoma of the uterine cervix. The acute toxicity was significantly greater among the patients receiving hyperthermia, and the survival was significantly worse among the Stage IIb patients receiving hyperthermia even though there was no difference in the local control rate.

In a randomized controlled trial, Franckena et al. (2008) evaluated long-term results of the Dutch Deep Hyperthermia Trial after 12 years of follow-up. The Dutch Deep Hyperthermia Trial showed that combining radiotherapy (RT) with hyperthermia (HT) improved three-year local control rates of 41–61%, as reported in an earlier study. From 1990–1996, a total of 114 women with locoregionally advanced cervical carcinoma were randomly assigned to RT or RT + HT. A total of 80% of the women had FIGO Stage IIIB or IVA tumor, 70% positive pelvic lymph nodes, tumor diameter ≥ 6 cm in 77% of the women. Radiotherapy was given in the recruiting institute, and for their weekly HT treatment, patients were referred to one of three institutes with HT facilities. One center used the BSD-2000 system, BSD Medical (Salt Lake City, UT). In the other centers, custom-built systems were used: a four-waveguide applicator system, and a Coaxial TEM applicator. Deep locoregional HT was prescribed once weekly to a total of five 90 minute sessions during the 5 weeks of external beam RT. The HT was given once weekly. The primary end point was local control. Secondary end points were overall survival and late toxicity. Differences with $p < 0.05$ were considered significant. At the 12-year follow-up, local control remained better in the RT + HT group (37% versus 56%; $p = 0.01$). Survival was persistently better after 12 years: 20% (RT) and 37% (RT + HT; $p = 0.03$). The difference in the cumulative incidence of Grades 3–5 radiation-induced toxicities in both groups of patients was not statistically significant ($p = 0.281$). The authors reported that RT + HT should be considered for patients with locally advanced cervical cancer and even more so if they are not suited to receive chemotherapy. However, in many countries, the option of HT is not considered or even available as an equivalent alternative for chemotherapy.

Non-Small Cell Lung Cancer: Mitsumori et al. (2007) conducted a multi-center prospective randomized trial to evaluate whether the combination of regional hyperthermia and radiotherapy improved the rate of local control compared to that obtained by radiotherapy alone. A total of 80 patients with locally advanced non-small cell lung cancer (NSCLC) were randomized to receive either standard radiation therapy alone or radiation therapy combined with hyperthermia. The primary endpoint was the local response rate. The secondary endpoints were local progression-free survival and overall survival. The median follow-up period was 204 days for all patients and 450 days for surviving patients. There were no significant differences between the two arms with regard to local response rate or overall survival rate. However, local progression-free survival was better in the radiation and hyperthermia arm. Toxicity was generally mild and no grade 3 late toxicity was observed in either arm. The authors reported that this study failed to show any substantial benefit from the addition of hyperthermia to radiotherapy in the treatment of locally advanced NSCLC.

Soft Tissue Sarcoma: The European Society for Hyperthermic Oncology (ESHO) and European Organization for Research and Treatment of Cancer (EORTC)–Soft Tissue and Bone Sarcoma Group (STBSG) 62961 conducted a multicenter, randomized phase 3 study to assess the efficacy and safety of adjuvant chemotherapy with regional hyperthermia in patients with localized high-risk soft tissue (STS) (Issels, et al., 2010). Eligible individuals were recruited from nine centers in four countries (six centers in Germany, one in Norway, one in Austria, one in the USA). Eligible patients were 18–70 years of age and had adult-type STS with the following risk criteria: Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grade 2 or 3, tumor diameter ≤ 5 cm, deep to the fascia, and no evidence of distant metastases. Patients were enrolled with primary or recurrent disease. In patients who had undergone previous surgery (tumor-free margins ≤ 1 cm or margins contaminated), random allocation to treatment was allowed within eight weeks of surgery. Patients were randomly assigned to either chemotherapy consisting of etoposide, ifosfamide, and doxorubicin (EIA) alone ($n = 169$), or EIA combined with regional hyperthermia by block randomization ($n = 172$). Block randomization was done centrally at the EORTC data center, with stratification according to site (extremity versus non-extremity), presentation of tumor (primary versus recurrent versus prior surgery), and center. Regional hyperthermia aiming for tumor temperatures of 42°C for 60 minutes were given on day 1 and 4 of each EIA cycle during both induction and post-induction therapy. The BSD-2000 hyperthermia system (BSD Medical Corporation, Salt Lake City, UT, USA) was used. Treatment was stopped or omitted if severe adverse events occurred. After

randomization, follow-up forms documenting toxicity and recurrence status were required every three months during the first year, every four months up to three years, every six months up to five years, and yearly thereafter. The primary outcome was local progression-free survival (LPFS), defined as the time from randomization to confirmed local progression, relapse, or death, whichever occurred first and irrespective of any occurrence of distant metastases. Secondary endpoints were disease-free survival (DFS), overall survival (OS), tumor response after induction therapy, treatment toxicity, and long-term complications. DFS was defined as the time from randomization to confirmed local failure, distant metastases, or death due to disease or treatment, whichever occurred first. After a median follow-up of 34 months, 132 patients had local progression (56 EIA plus regional hyperthermia versus 76 EIA). Patients were more likely to experience local progression or death in the EIA-alone group compared with the EIA plus regional hyperthermia group (relative hazard [RH] 0.58, 95% CI 0.40–1–0.83; $p=0.03$), with an absolute difference in LPFS at two years of 15% (95% CI 6–26; 76% EIA plus regional hyperthermia versus 61% EIA). For disease-free survival the relative hazard was 0.70 (95% CI 0.54–0.92, $p=0.011$) for EIA plus regional hyperthermia compared with EIA alone. The treatment response rate in the group that received regional hyperthermia was 28.8%, compared with 12.7% in the group who received chemotherapy alone ($p=0.002$). In a prespecified per-protocol analysis of patients who completed EIA plus regional hyperthermia induction therapy compared with those who completed EIA alone, overall survival was better in the combined therapy group (HR 0.66, 95% CI 0.45–0.98, $p=0.038$). There was no evidence of a difference in overall survival between the EIA-alone group and the combined treatment group. The authors report this could be due to the low power to detect any difference because of the relatively few deaths so far (153 patients). Leucopenia (grade 3 or 4) was more frequent in the EIA plus regional hyperthermia group compared with the EIA-alone group (128 of 165 versus 106 of 167, $p=0.005$). Hyperthermia-related adverse events were pain, bolus pressure, and skin burn, which were mild to moderate in 66 (5%), 43 (4%), and 29 patients (8%), and severe in seven (43%), eight (9%), and one patient (6%), respectively. Two deaths were attributable to treatment in the combined treatment group, and one death was attributable to treatment in the EIA-alone group. The authors report that whether a similar benefit will be seen in lower risk patients, and whether the safety profile will be the same, and hence the trade off between benefit and harm worthwhile, remains to be established.

Cochrane Reviews

Cervical Cancer: In a Cochrane Review, Lutgens et al. (2010) assessed whether adding hyperthermia to standard radiotherapy for locally advanced cervix carcinoma (LACC) has an impact on (1) local tumor control, (2) survival and (3) treatment related morbidity. Randomized controlled trials (RCTs) comparing radiotherapy alone versus combined hyperthermia and radiotherapy in patients with LACC. Between 1987 and 2009 the results of six RCTs were published, and used for the review (Vasanthan, et al., 2005; van der Zee, et al., 2000; Sharma, et al., 1991; Chen, et al., 1997; Harima, et al., 2001; Datta, et al., 1987). Various modalities were used to deliver the energy for hyperthermia treatment. The sequencing of radiotherapy and hyperthermia and the interval between radiotherapy and hyperthermia differed between and within the studies. Primary endpoints were complete response rate following treatment, local recurrence, overall survival and treatment related toxicity grade 3 to 4 indicates a significant improvement of local (pelvic) tumor control and overall survival for the combined treatment modality (RHT) whereas acute and late toxicity was not significantly different between both treatment groups. Complete tumor response at the end of treatment in the pooled data analysis including 267 study patients (Datta 1987; Chen 1997; van der Zee 2000; Harima 2001) yields a significantly better treatment outcome following combined RHT (RR 0.56 (95% CI 0.39 to 0.79); $p<0.001$). Local recurrence as endpoint in the pooled data analysis including 264 study patients (van der Zee 2000; Harima 2001; Vasanthan 2005) yields a significantly reduced local recurrence rate (HR 0.48 (95%CI 0.37 to 0.63); $p<0.001$). Overall survival as endpoint in the pooled data analysis including 264 study patients (van der Zee 2000; Harima 2001; Vasanthan 2005) yielded a significantly better survival for the combined treatment group (RHT) (HR 0.67; 95% CI 0.45 to 0.99; $p=0.05$). The authors conclusions stated that “The limited number of patients available for analysis, methodological flaws and a significant over-representation of patients with FIGO stage IIIB prohibit drawing definite conclusions regarding the impact of adding hyperthermia to standard radiotherapy. However, available data do suggest that the addition of hyperthermia improves local tumor control and overall survival in patients with locally advanced cervix carcinoma without affecting treatment related grade 3 to 4 acute or late toxicity.”

Rectal Cancer: In a Cochrane Review, De Haas-Kock et al. (2009) conducted a systematic review of the literature to study the additional value of hyperthermia if added to radiotherapy in advanced rectal cancer, with respect to pathological complete responses, overall survival and toxicity in rectal cancer therapy. Radiotherapy with or without chemotherapy followed by surgery has become standard treatment for advanced rectal cancer. Criteria for considering studies for this review included the outcome measures studied including: overall survival

(OS) at 2, 3, 4 and 5-year; local tumor recurrence at 2 and 3 years; severe acute tissue toxicity and severe late tissue toxicity, severe toxicity is defined as grade 3-4 toxicity and complete tumor response (CR) at 2 months. Complete tumor response (CR) is defined as disappearance of clinical symptoms or as tumor free margins (R0 resections) in operated patients. Only phase II and III randomised controlled clinical trials were included in the analysis. Six RCTs published between 1990 and 2007 were identified (Berdov, et al., 1990, 1996; Kakehi, et al., 1990; You, et al., 1993; Trotter, et al., 1996; van der Zee, et al., 2000). A total number of 520 patients were treated, 258 in the radiotherapy only arm (RT) and 262 in the radiotherapy-hyperthermia arm (RHT). The authors used these definitions for advanced and recurrent rectal cancer: UICC stage T3-4 and/or N+M0; recurrent rectal cancer a palpable or visible presacral mass. The type of interventions included any regimen of pelvic radiotherapy given concurrently or not with a specific hyperthermia regimen. The studies included hyperthermia treatment that was administered regionally, intracavitary or interstitially. Only studies which used a minimum temperature of 41 degrees Celsius for hyperthermia were included. Four studies (424 patients) reported overall survival (OS) rates. After two years, OS was significantly better in the RHT group (p=0.001), but this difference disappeared after a longer period (3, 4 and 5 year OS). All but one studies reported CR rates. A significant higher CR rate was observed in the RHT group (p=0.01). Only two studies reported on acute toxicity. In these two studies no significant differences in acute toxicity were observed between the RT and the RHT group. Due to limited data the authors were not able to draw firm conclusion about acute or late toxicity. In a review of the available studies the authors reported that the overall quality of studies published is poor, prohibiting definitive conclusions regarding the beneficial effect of hyperthermia added to standard radiotherapy. However, the authors reported that adding hyperthermia to radiation in locally advanced and recurrent rectal cancer, can lead to higher short term local/pelvic control rates and a short term survival benefit. There is limited data available regarding acute and long term morbidity. The authors' conclusions stated that "Further studies are needed to compare chemoradiation versus thermoradiation versus chemoradiation plus hyperthermia in well selected/conducted and quality controlled randomised trials."

Literature Review Whole Body Hyperthermia (WBH): Clinical studies evaluating WBH are primarily in the form of uncontrolled clinical trials from Germany and the Netherlands. There were also some early pilot studies from a group of researchers at the University of Wisconsin-Madison, one of which was partially randomized (Robins, et al., 1993; Robins, et al., 1997). The study populations were generally small and were heterogeneous with respect to disease, site, stage and prior therapy. However, study inclusion criteria generally specified that patients must have histologically confirmed advanced or metastatic malignancy that was unresponsive to other treatment methods and normal organ function, apart from metastatic disease. Treatment protocols varied among the studies. In general, the larger studies assessed hyperthermia as an adjunct to chemotherapy, with outcome measures that evaluated complications of treatment, and tumor and clinical response. Duration of follow-up varied from several months to several years. Studies evaluating the use of WBH as an adjunct to radiation therapy are lacking. (Brockow, et al., 2007; Hildebrandt, et al., 2005; Richel, et al., 2004; Douwes, et al., 2004; Westermann, et al., 2001; Hildebrandt, et al., 2004; Hegewisch-Becker, et al., 2002; Wiedemann, et al. 1996; Robins, et al., 1995; Pontiggia, et al., 1995; Wiedemann, et al., 1994).

Professional Societies/Organizations:

National Comprehensive Cancer Network[®] (NCCN[®]): The National Comprehensive Cancer Network[®] (NCCN[®]) Clinical Practice Guidelines in Oncology[™] mention hyperthermia in two guidelines that address breast cancer and soft tissue sarcoma. At this time, hyperthermia treatment was not mentioned in other NCCN Clinical Practice Guideline in Oncology[™] (e.g., melanoma, head and neck, prostate, bladder, cervical, colon, anal, esophageal, gastric, hepatobiliary, kidney, ovarian, thyroid, appendix, endometrial, peritoneal lining, small cell lung, non-small cell lung, testicular, uterine neoplasms, non-melanoma skin cancers).

The NCCN[®] Clinical Practice Guidelines in Oncology[™] Rectal Cancer mentions perioperative hyperthermic intraperitoneal chemotherapy. The guideline does not discuss other modalities of hyperthermia treatment (NCCN, 2010a).

The NCCN[®] Clinical Practice Guidelines in Oncology[™] Breast Cancer indicates that consideration of the addition of hyperthermia to irradiation for localized recurrences/metastasis (category 3) was considered. The guideline states that there have been several prospective randomized trials comparing radiation to radiation plus hyperthermia in the treatment of locally advanced/recurrent cancers, primarily breast cancer chest wall recurrences (citing Vernon et al., 1996 and Jones et al., 2005). NCCN reports that while "there is heterogeneity among the study results, a recent series with strict quality assurance demonstrated a statistically significant increase in local tumor response and greater duration of local control with the addition of hyperthermia to

radiation compared to radiation alone (Jones, et al., 2005). No differences in overall survival have been demonstrated. Delivery of local hyperthermia is technically demanding and requires specialized expertise and equipment (eg, the monitoring of temperatures and management of possible tissue burns). The Panel thus recommends that the use of hyperthermia be limited to treatment centers with appropriate training, expertise, and equipment. The addition of hyperthermia generated substantial discussion and controversy among the Panel and is a category 3 recommendation." A category 3 is defined as major NCCN disagreement among the panel members representing different institutions (NCCN, 2010b).

The NCCN[®] Clinical Practice Guidelines in Oncology™ Soft Tissue Sarcoma reports from a 2007 meeting abstract that "Interim overall survival data are encouraging from an ongoing Phase III trial (European Organization Research and Treatment of Cancer [EORTC]-62961) of regional hyperthermia versus chemotherapy with EIA (etoposide, ifosfamide, and adriamycin) alone for patients with locally advanced high-risk STS, especially for extremity sarcomas." The guideline addresses another ongoing EORTC Phase III trial, Issels et al. (2002). "After a median follow-up of 24.9 months, disease free survival (31.7 months versus 6.2 months, respectively), local progression free survival (84% versus 64% respectively for extremity sarcomas and 57% versus 39% respectively for body wall and abdominal sarcomas) and overall response rate 28.7% versus 12.6% respectively, were significantly superior for patients treated with EIA plus regional hyperthermia to those treated with EIA alone" (NCCN, 2010c).

American College of Radiology (ACR): The 2009 ACR Practice Guideline for Radiation Oncology mentions hyperthermia under the subsection "Other Treatment Modalities" stating that, "Other treatment modalities are sometimes combined with external photon beams or brachytherapy to enhance the antitumor effects and decrease the effects on surrounding normal tissues. Examples include hyperthermia, photodynamic therapy, and the use of unsealed-source radioisotopes."

The 2008 ACR Appropriateness Criteria[®] on recurrent rectal cancer mentions hyperthermia in the summary of literature review under the subsection hyperfractionated external beam radiation stating, "Juffermans et al reported a 72% good or complete palliative effect for a median of 6 months in patients receiving reirradiation and hyperthermia." Hyperthermia is not mentioned as a treatment in the Variant examples (ACR, 2008). The Juffermans study is a feasibility study. The authors of the study reported that "The results of our study do not allow final conclusions on the additional value of hyperthermia in the treatment of patients with recurrent, previously irradiated colorectal carcinoma, because this study did not include a control group of patients who were treated with reirradiation alone" (Juffermans, et al, 2003).

The 2007 ACR Appropriateness Criteria[®] on locally advanced breast cancer mentions hyperthermia in the summary of literature review under the subsection timing, techniques, treatment modalities under study stating that hyperthermia has been studied to enhance radiation effects in locally advanced and recurrent breast cancer. Hyperthermia is not mentioned as a treatment in the Variant examples.

The 2006 ACR Appropriateness Criteria[®] on local regional recurrence (LR) and salvage surgery–breast cancer rates hyperthermia plus radiation as a six for locoregional recurrence of breast cancer in a patient with multiple recurrent nodules along a mastectomy scar; this is lower than radiation therapy alone (rated as a seven), where nine is the most appropriate treatment (ACR, 2006). Hyperthermia is not discussed in the summary of literature.

American Cancer Society (ACS): The ACS states, "while hyperthermia is a promising way to enhance cancer treatment, it is largely an experimental technique at this time and is not commonly used in cancer treatment. Many clinical trials of hyperthermia are now under way to try to determine the best way to use this technique. Current studies are gauging its usefulness against the following cancers (e.g., breast, cervical, colorectal [spread to liver], endometrial, kidney, liver, lung, ovarian, pancreas, prostate, sarcomas [soft tissue cancers], and thyroid)" (ACS, 2008).

The National Cancer Institute (NCI): The NCI Fact Sheet on Hyperthermia in Cancer Treatments states, "A number of challenges must be overcome before hyperthermia can be considered a standard treatment for cancer. Many clinical trials are being conducted to evaluate the effectiveness of hyperthermia. Some trials continue to research hyperthermia in combination with other therapies for the treatment of different cancers. Other studies focus on improving hyperthermia techniques" (NCI, 2004).

The American College of Surgeons Oncology Group, the American Society for Therapeutic Radiology and Oncology, the American Society of Clinical Oncology, and the American College of Surgeons Oncology Group do not have professional society opinion or guidelines on hyperthermia treatment for cancer.

Summary

There is limited evidence from randomized controlled or comparative clinical trials in the peer-reviewed literature to support the safety and efficacy of local external superficial hyperthermia when used in combination with radiation therapy for treatment of locally advanced and recurrent breast cancer for the treatment of patients who have failure, intolerance or contraindication to conventional therapy. The overall body of evidence suggests that local external superficial hyperthermia, when used as part of a multimodal regimen, may aid in increasing local tumor response and greater duration of local. This does not consistently translate into increased survival rates.

Evidence in the peer-reviewed literature on the safety and efficacy of local interstitial, local endocavitary, or regional deep hyperthermia as an adjunctive treatment for various types of cancer have failed to provide guidance for patient selection, protocols or timing regimens that could be standardized and safely applied. The effectiveness of these hyperthermia treatments has not been shown to improve short- or long-term patient treatment outcomes and survival rates in comparison to standard adjuvant radiation therapy and/or administration of systemic chemotherapy.

The available evidence, which comes from a limited number of small, uncontrolled studies, suggests that whole body hyperthermia (WBH) may enhance clinical response to chemotherapy in some patients who have refractory advanced cancer. However, an accurate assessment of the treatment effect of WBH cannot be made on the basis of these studies; the absence of control groups, small sample sizes, heterogeneity in patient populations and differences in treatment protocol and outcome measures preclude definitive conclusions regarding the efficacy of WBH as an adjunct to chemotherapy or radiotherapy.

A number of complications specifically relating to extracorporeal WBH have been reported, including pulmonary edema, arrhythmias, liver necrosis, peripheral neuropathy, transverse myelitis, seizures, rhabdomyolysis, anemia, leucopenia, renal dysfunction, hemorrhage, protracted diarrhea, anasarca, hepatitis, coagulopathies, electrolyte abnormalities, pressure sores and infection.

Definitive selection criteria for the use of WBH in patients with cancer have not been established. In view of the lack of evidence from well-designed randomized control trials designed to evaluate the safety and efficacy of this technology, the role of WBH as a treatment for cancer has not yet been established.

Coding/Billing Information

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

Covered when medically necessary when used to report local external superficial hyperthermia when used as an adjunct to radiation therapy for the diagnoses noted below:

CPT [®] * Codes	Description
77600 [†]	Hyperthermia, externally generated; superficial (ie, heating to a depth of 4 cm or less)

ICD-9-CM Diagnosis Codes	Description
174.0-174.9	Malignant neoplasm of female breast
175.0-175.9	Malignant neoplasm of male breast
198.81	Secondary malignant neoplasm of other specified sites, Breast

Experimental/Investigational/Unproven/Not Covered when used to report hyperthermia when used as an adjunct to radiation therapy:

CPT^{®*} Codes	Description
77605 [†]	Hyperthermia, externally generated; deep (ie, heating to depths greater than 4 cm)
77610 [†]	Hyperthermia generated by interstitial probe(s); 5 or fewer interstitial applicators
77615 [†]	Hyperthermia generated by interstitial probe(s); more than 5 interstitial applicators
77620 [†]	Hyperthermia generated by intracavitary probe(s)

ICD-9-CM Diagnosis Codes	Description
	All other codes

[†]**Note:** This policy does not address hyperthermia used as an adjunct to chemotherapy.

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	6/15/2007	0098	Whole Body Hyperthermia Treatment For Cancer

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