Healthy Blue

Clinical UM Guideline

Subject:	Hyperthermia for Cancer Therapy		
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Description

This document addresses hyperthermia for cancer therapy. Hyperthermia is a type of cancer treatment in which body tissue is exposed to high temperatures using external and internal heating devices. Hyperthermia is routinely used with other forms of cancer therapy. Hyperthermia may make cancer cells more sensitive to chemotherapy and radiation therapy or harm other cancer cells radiation cannot damage.

Note: This document does not address hyperthermic intraperitoneal chemotherapy (HIPEC), hyperthermic limb perfusion, radiofrequency ablation to treat tumors outside the liver or locally ablative techniques for treating primary and metastatic liver malignancies.

For information regarding radiofrequency ablation to treat tumors outside the liver or locally ablative techniques for treating primary and metastatic liver malignancies see the following documents:

- CG-SURG-62 Radiofrequency Ablation to Treat Tumors Outside the Liver
- CG-SURG-78 Locally Ablative Techniques for Treating Primary and Metastatic Liver Malignancies

Clinical Indications

Medically Necessary:

Local hyperthermia, using either external or interstitial modalities, in combination with radiation therapy is considered medically necessary for the treatment of individuals with primary or metastatic cutaneous or subcutaneous superficial tumors (for example, superficial recurrent melanoma, chest wall recurrence of breast cancer, and cervical lymph node metastases from head and neck cancer).

Treatment should be limited to twice weekly treatments for 5 weeks (10-12 total treatments).

Not Medically Necessary:

Local hyperthermia, using either external or interstitial modalities, in conjunction with radiation therapy is considered **not medically necessary** for all other uses not identified as medically necessary.

Intraluminal/endocavitary hyperthermia is considered **not medically necessary** in the treatment of malignancies.

Regional deep tissue hyperthermia is considered **not medically necessary** in the treatment of malignancies.

Whole-body hyperthermia is considered **not medically necessary** in the treatment of malignancies.

Hyperthermia in conjunction with chemotherapy is considered **not medically necessary.**

Coding

The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Local hyperthermia (superficial external, interstitial)

CPT

77600	Hyperthermia, externally generated; superficial (ie, heating to a depth of 4 cm or less)
77610	Hyperthermia generated by interstitial probe(s); 5 or fewer interstitial applicators
77615	Hyperthermia generated by interstitial probe(s); more than 5 interstitial applicators

ICD-10 Procedure

D0Y78ZZ	Hyperthermia of peripheral nerve
D7Y38ZZ	Hyperthermia of neck lymphatics
D7Y48ZZ	Hyperthermia of axillary lymphatics
D7Y88ZZ	Hyperthermia of inguinal lymphatics
DBY78ZZ	Hyperthermia of chest wall
DHY28ZZ	Hyperthermia of face skin
DHY38ZZ	Hyperthermia of neck skin
DHY48ZZ	Hyperthermia of arm skin
DHY68ZZ	Hyperthermia of chest skin
DHY78ZZ	Hyperthermia of back skin
DHY88ZZ	Hyperthermia of abdomen skin
DHY98ZZ	Hyperthermia of buttock skin
DHYB8ZZ	Hyperthermia of leg skin
DMY08ZZ	Hyperthermia of left breast
DMY18ZZ	Hyperthermia of right breast
DWY18ZZ	Hyperthermia of head and neck
DWY28ZZ	Hyperthermia of chest
DWY38ZZ	Hyperthermia of abdomen
DWY68ZZ	Hyperthermia of pelvic region

ICD-10 Diagnosis

C00.0-C14.8	Malignant neoplasm of lip, oral cavity and pharynx

C43.0-C43.9	Malignant melanoma of skin
C4A.0-C4A.9	Merkel cell carcinoma
C44.00-C44.99	Other malignant neoplasm of skin
C49.0-C49.9	Malignant neoplasm of other connective and soft tissue
C50.011-C50.929	Malignant neoplasm of breast
C76.1	Malignant neoplasm of thorax
C77.0	Secondary and unspecified malignant neoplasm of lymph nodes of head, face and neck
C79.2	Secondary malignant neoplasm of skin
C79.81	Secondary malignant neoplasm of breast
C79.89	Secondary malignant neoplasm of other specified sites [chest wall]
D03.0-D03.9	Melanoma in situ
D04.0-D04.9	Carcinoma in situ of skin
D09.8	Carcinoma in situ of other specified sites

Other hyperthermia (deep, intracavitary, whole body)
Note: the following procedures are considered not medically necessary for all indications:

CPT

77605	Hyperthermia, externally generated; deep (ie, heating to depths greater than 4 cm)
77620	Hyperthermia generated by intracavitary probe(s)

ICD-10 Procedure

D0Y08ZZ	Hyperthermia of brain
D0Y18ZZ	Hyperthermia of brain stem
D0Y68ZZ	Hyperthermia of spinal cord
D7Y08ZZ	Hyperthermia of bone marrow
D7Y18ZZ	Hyperthermia of thymus
D7Y28ZZ	Hyperthermia of spleen
D7Y58ZZ	Hyperthermia of thorax lymphatics
D7Y68ZZ	Hyperthermia of abdomen lymphatics
D7Y78ZZ	Hyperthermia of pelvis lymphatics
D8Y08ZZ	Hyperthermia of eye
D9Y08ZZ	Hyperthermia of ear
D9Y18ZZ	Hyperthermia of nose
D9Y38ZZ	Hyperthermia of hypopharynx
D9Y48ZZ	Hyperthermia of mouth
D9Y58ZZ	Hyperthermia of tongue
D9Y68ZZ	Hyperthermia of salivary glands
D9Y78ZZ	Hyperthermia of sinuses
D9Y88ZZ	Hyperthermia of hard palate
D9Y98ZZ	Hyperthermia of soft palate
D9YB8ZZ	Hyperthermia of larynx
D9YD8ZZ	Hyperthermia of nasopharynx

D9YF8ZZ	Hyperthermia of oropharynx
DBY08ZZ	Hyperthermia of trachea
DBY18ZZ	Hyperthermia of bronchus
DBY28ZZ	Hyperthermia of lung
DBY58ZZ	Hyperthermia of pleura
DBY68ZZ	Hyperthermia of mediastinum
DBY88ZZ	Hyperthermia of diaphragm
DDY08ZZ	Hyperthermia of esophagus
DDY18ZZ	Hyperthermia of stomach
DDY28ZZ	Hyperthermia of duodenum
DDY38ZZ	Hyperthermia of jejunum
DDY48ZZ	Hyperthermia of ileum
DDY58ZZ	Hyperthermia of colon
DDY78ZZ	Hyperthermia of rectum
DFY08ZZ	Hyperthermia of liver
DFY18ZZ	Hyperthermia of gallbladder
DFY28ZZ	Hyperthermia of bile ducts
DFY38ZZ	Hyperthermia of pancreas
DGY08ZZ	Hyperthermia of pituitary gland
DGY18ZZ	Hyperthermia of pineal body
DGY28ZZ	Hyperthermia of adrenal glands
DGY48ZZ	Hyperthermia of parathyroid glands
DGY58ZZ	Hyperthermia of thyroid
DPY08ZZ	Hyperthermia of skull
DPY28ZZ	Hyperthermia of maxilla
DPY38ZZ	Hyperthermia of mandible
DPY48ZZ	Hyperthermia of sternum
DPY58ZZ	Hyperthermia of rib(s)
DPY68ZZ	Hyperthermia of humerus
DPY78ZZ	Hyperthermia of radius/ulna
DPY88ZZ	Hyperthermia of pelvic bones
DPY98ZZ	Hyperthermia of femur
DPYB8ZZ	Hyperthermia of tibia/fibula
DPYC8ZZ	Hyperthermia of other bone
DTY08ZZ	Hyperthermia of kidney
DTY18ZZ	Hyperthermia of ureter
DTY28ZZ	Hyperthermia of bladder
DTY38ZZ	Hyperthermia of urethra
DUY08ZZ	Hyperthermia of ovary
DUY18ZZ	Hyperthermia of cervix
DUY28ZZ	Hyperthermia of uterus
DVY08ZZ	Hyperthermia of prostate

DVY18ZZ	Hyperthermia of testis
DWY48ZZ	Hyperthermia of hemibody
DWY58ZZ	Hyperthermia of whole body

ICD-10 Diagnosis

All diagnoses

Discussion/General Information

Hyperthermia is a type of cancer treatment in which body tissue is exposed to high temperatures using external and internal heating devices. Early clinical studies suggest tumor cells may be more sensitive to increased temperature as compared with normal cells, that heat may enhance the tumoricidal effects of radiation or chemotherapy and overcome acquired drug resistance, and that elevated temperatures can stimulate certain components of the immune system, which may aid in destroying cancer cells. A number of methods of hyperthermia are currently under study, including local, regional, and whole-body hyperthermia.

Local Hyperthermia in Conjunction with Radiation Therapy for Superficial Malignancies

In local hyperthermia, heat is applied to a small area, such as a tumor, using various techniques that deliver energy to heat the tumor. Different types of energy may be used to apply heat, including microwave, radiofrequency, and ultrasound. Depending on the tumor location, there are several approaches to local hyperthermia. External approaches are used to treat tumors in or just below the skin. External applicators are positioned around or near the tumor, and energy is focused on the tumor to raise the temperature. Interstitial techniques are used to treat tumors deep within the body, such as brain tumors. This technique allows the tumor to be heated to higher temperatures than external techniques. Radiofrequency ablation is a type of interstitial hyperthermia using radio waves to heat and kill cancer cells.

A literature search focused on randomized controlled trials of hyperthermia in superficial malignancies. A variety of studies were published in the 1990s that examined the role of hyperthermia in breast cancer (Vernon, 1996), melanoma (Overgaard, 1995), head and neck cancer (Datta, 1990; Emami, 1996; Valdagni, 1994) and a variety of superficial tumors (Perez, 1991). Not all trials reported positive results, presumably in part related to the difficulty in delivering consistent thermal doses.

Jones and colleagues (2005) reported on a trial of 109 individuals, with a variety of different types of superficial tumors, who were randomized to receive radiation therapy with or without a well-defined and consistent dose of hyperthermia. The majority had breast cancer with chest wall involvement. Other groups included those with head and neck cancer and melanoma. Hyperthermia was associated with significantly improved local control (66%) compared to the control group (42%) (p=0.02). Survival was not significantly different between the two groups.

One of the most common superficial tumors is breast cancer. Vernon (1996) published a combined analysis of five randomized trials initiated between 1988 and 1991. A total of 306 individuals were randomized to receive radiation

therapy with or without hyperthermia. The primary outcome was complete response rate, which was achieved in 59% of those receiving hyperthermia compared to 41% in the control group.

The National Comprehensive Cancer Network (NCCN) (2018) clinical practice guideline on breast cancer indicates that hyperthermia is a category 3 recommendation when used in conjunction with radiation therapy in individuals with locally recurrent/metastatic breast cancer. A category 3 is defined as major NCCN disagreement among the panel members representing different institutions.

Intraluminal/Endocavitary Hyperthermia in Conjunction with Radiation Therapy

Intraluminal or endocavitary methods may be used to treat tumors within or near body cavities, such as the esophagus or rectum. Probes are placed inside the cavity and inserted into the tumor to deliver energy and heat the area directly.

The Dutch Deep Hyperthermia trial was a randomized study designed to evaluate the role of once weekly hyperthermia in 114 women with locally advanced cervical cancer (Stage IIB, IIIB or IV). Franckena (2008) published long-term results (12-year) in which the primary end point was local control. Local control was improved in the hyperthermia group compared to the control group (56% vs 37%; p=0.01). Additionally, the improved local control translated to improved survival rates at 12 years (37% vs 20%; p=0.03). The toxicities were similar in both groups. The same group of authors, Franckena (2009), reported on the outcomes of hyperthermia in a prospective case series of 378 individuals with locally advanced cervical cancer. The complete response, local control, and survival rates were similar to the results in the randomized Dutch Deep Hyperthermia Trial. The authors concluded that radiation in conjunction with hyperthermia can be considered as an alternative to chemoradiation therapy in those with locally advanced cervical cancer. However, in the United States, the standard treatment of locally advanced cervical cancer is chemoradiation, and there is inadequate data comparing radiation and hyperthermia to this standard treatment.

The Dutch Deep Hyperthermia trial also enrolled individuals with bladder cancer. An initial improvement in local control rates disappeared during follow up (van der Zee, 2000).

A Cochrane Review (Lutgens, 2010), assessed the role of hyperthermia as an adjunct to radiotherapy in the treatment of locally advanced cervix cancer. The authors reported:

> The limited number of patients available for analysis, methodological flaws and a significant over-representation of patients with stage IIIB prohibit drawing definite conclusions regarding the impact of adding hyperthermia to standard radiotherapy.

Regional, Whole Body or Deep Tissue Hyperthermia in Conjunction with Radiation Therapy

In regional hyperthermia, various approaches may be used to heat large areas of tissue, such as a body cavity, organ, or limb. Regional deep tissue hyperthermia may be used to treat cancers within the body, such as cervical or bladder cancer. External applicators are positioned around the body cavity or organ to be treated, and microwave or radiofrequency energy is focused on the area to raise its temperature.

Whole body hyperthermia (WBH) has been proposed as a therapy, most commonly as an adjunct to radiotherapy or chemotherapy, to treat metastatic cancer that has spread throughout the body. WBH is achieved with either radiant heat or extracorporeal technologies that raise the body temperature to 107-108°F. In radiant WBH, heat is externally applied to the whole body using hot water blankets, hot wax, inductive coils, or thermal chambers. The individual is sedated throughout the WBH procedure, which lasts approximately 4 hours. Extracorporeal WBH is achieved by re-infusion 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 re-injected into a major vein. The desired body temperature is adjusted and controlled by changing the volume flow of the warmed re-infused blood. Extracorporeal hyperthermia treatments are conducted under general anesthesia.

A literature search focusing on randomized controlled trials identified a single study of regional hyperthermia with radiation therapy in 80 individuals with non-small cell lung cancer (Mitsumori, 2007). This trial failed to show any substantial benefit from the addition of hyperthermia to radiotherapy in the treatment of locally advanced non-small cell lung cancer. The literature search did not identify any randomized studies of deep tissue hyperthermia.

Hyperthermia in Conjunction with Chemotherapy with or without Radiation Therapy

Issels and colleagues (2010) reported on a parallel-group randomized controlled trial designed to assess the safety and efficacy of neo-adjuvant regional hyperthermia in conjunction with chemotherapy. A total of 341 individuals were enrolled in the trial between July 21, 1997 and November 30, 2006 at nine European and North American centers. Individuals with localized high-risk soft tissue sarcoma were randomly assigned to receive either chemotherapy consisting of etoposide, ifosfamide, and doxorubicin (EIA) alone (n=172), or combined with regional hyperthermia (EIA plus regional hyperthermia) (n=169) in addition to local therapy. Of all the enrollees, 151 subjects (89.3%) in the EIA plus regional hyperthermia group and 146 (84.9%) in the EIA alone group completed induction chemotherapy. In the combined treatment group, 129 subjects (76.3%) received seven to eight regional hyperthermia treatments, 33 (19.5%) received one to six regional hyperthermia treatments, and 7 (4.1%) received none. Most of the study subjects (90.6%) also underwent surgery (155 EIA plus regional hyperthermia vs 154 EIA alone). Approximately two-thirds of the individuals underwent a tumor resection and others underwent amputation. A total of 108 subjects in the combined treatment group and 106 in the EIA alone group received radiotherapy; 61 subjects in the combined treatment group and 64 in the EIA alone group did not receive radiotherapy. The primary reason for not receiving radiotherapy was an abdominal or retroperitoneal tumor location. More subjects in the combined treatment group completed full post-induction chemotherapy as compared to the EIA alone group (89 [52.7%] vs 71 [41.3%]; p=0.020). A similar number did not receive post-induction therapy (43 in the combined treatment group vs 47 in the EIA alone group) due to non-compliance. Also, in the combined treatment group 60 subjects (35.5%) received seven to eight regional hyperthermia treatments, 28 (16.6%) received one to six regional hyperthermia treatments and 66 did not receive any regional hyperthermia. Reasons for not receiving regional hyperthermia were side effect related or intolerance to heat treatment. The overall duration of study treatment was 32.4 weeks for the combined treatment group versus 29.1 weeks in the EIA alone group. The primary outcome of the study was local progression-free survival which was 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, overall survival, tumor response after induction therapy, treatment toxicity, and long-term complications.

Subjects were observed as 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% confidence interval [CI], 0.41-0.83; p=0.003). 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). After a median follow-up time of 34 months, 132 subjects had local progression (56 EIA plus regional hyperthermia vs 76 EIA). A total of 153 individuals died during the follow-up period of 128 months with 2 deaths attributed to treatment in the combined treatment group, and 1 death was attributed to treatment in the EIA alone group. A higher incidence of hematological toxicity (leukopenia 72.6% vs 63.5%, p=0.005) was noted in the combined therapy group compared with EIA alone. When all individuals who were assigned to treatment were analyzed, there was no evidence of a difference in overall survival between the EIA alone group and the combined treatment group. Among the 269 individuals who completed induction therapy (4 cycles EIA plus 8 regional hyperthermias vs 4 cycles EIA alone) there was a significant difference in overall survival in the combined therapy group compared with the EIA alone group (HR 0.66, p=0.038). The authors indicated that this was the first randomized phase 3 trial to show that regional hyperthermia increases the benefit of chemotherapy. Although study results may show promise, there is a need for additional controlled studies to confirm these early findings.

Chen and colleagues (2012) enrolled 358 individuals with malignant pleural effusion in a prospective randomized trial designed to evaluate the safety and efficacy of intrapleural chemotherapy consisting of cisplatin and OK-432 (picinbanil) plus hyperthermia. Two study groups across four Chinese cancer centers consisted of 179 subjects each. Those in group A received the intrapleural combination of cisplatin and OK-432 with hyperthermia, while Group B received the same intrapleural combination without hyperthermia. Quality of life scores increased in both groups as compared to prior treatment. The survival follow-up period varied from 3 to 24 months. A total of 26 subjects in group A and 24 in group B were lost to follow-up. The median survival in group A (8.9 months) and group B (6.2 months) were similar (p>0.05).

Several studies (Heijkoop, 2012; Westermann, 2012) have evaluated a triple combination therapy consisting of regional hyperthermia, chemotherapy and brachytherapy for the treatment of advanced cancer of the cervix. Westermann and colleagues (2012) enrolled 68 women with advanced cervical cancer in a small prospective registry study in the USA, Norway and the Netherlands. Treatment consisted of a triple combination of regional whole pelvis hyperthermia (four weekly sessions), chemotherapy (at least four courses of weekly cisplatin) and radiotherapy (brachytherapy and external beam radiotherapy). At a median follow-up of 81 months, tumors returned in 28 women resulting in 21 deaths. The 5-year recurrence-free survival in the study was 57.5% and 5-year overall survival was 66.1%. The authors indicated that survival results with the addition of whole pelvic HT to RT and chemotherapy for advanced cervical cancer were comparable to historical controls. This study was limited by a small size and lack of a concurrent control group.

Heijkoop and colleagues (2012) also studied triple combination therapy consisting of hyperthermia, chemotherapy, and radiotherapy in a pilot study of women with advanced stage cervical cancer. A total of 43 women were treated

with platinum-based chemotherapy, followed by radiotherapy, brachytherapy and five hyperthermia treatments. A total of 67% completed all six planned courses of chemotherapy. At the end of chemotherapy, 83.7% achieved a complete or partial response. At the end of treatment, the complete response rate was 81.4%. The median follow-up time was 29.8 months (range 4.1-124.8). Overall survival rate at 12 months was 79%. The authors recommended proceeding to a phase II trial to obtain additional information. This trial was limited by a small size and lack of a comparator.

Schroeder and colleagues (2012) evaluated the impact of regional hyperthermia with neoadjuvant chemoradiation on rates of complete pathological response (pCR) and sphincter-sparing surgery for locally advanced rectal cancer. Between 2007 and 2010, 106 individuals received treatment consisting of neoadjuvant chemoradiation either with (n=61) or without (n=45) regional hyperthermia in a non-randomized fashion. A retrospective comparison was performed between the two groups: 45 subjects received standard treatment consisting of 5040 cGy in 28 fractions to the pelvis and 5-fluorouracil (RCT group) and 61 subjects received the same treatment in combination with regional hyperthermia (HRCT group). A pCR occurred in 6.7% of the RCT group and in 16.4% of the HRCT group. Those who received at least four hyperthermia treatments (n=40) achieved a significantly higher pCR rate (22.5%) than the remaining 66 subjects (p=0.043). Rates of sphincter-sparing surgery were similar in both groups. The authors conclude that "a randomised trial comparing RCT and HRCT with well-defined inclusion criteria for high-risk patients is warranted."

A Phase II study combining hyperthermia concurrent with neoadjuvant chemoradiotherapy (nCRT) for advanced rectal cancer (Barsukov, 2013) enrolled 64 previously untreated individuals. Hyperthermia was combined with chemoradiotherapy and subsequent resection was performed in 59 subjects (92.2%). A total of 5 individuals (7.8%) were deemed inoperable. Median follow up was 24.9 months. The 2-year overall survival was 91% and 2-year disease-free survival was 83%. Study limitations include lack of randomization and lack of a control group.

Ranieri and colleagues (2017) published a prospective pilot study evaluating the efficacy, safety, and survival of anti-angiogenic-based chemotherapy associated to regional deep capacitive hyperthermia in metastatic cancer subjects. A total of 23 subjects with metastatic colorectal (n=16), ovarian (n=5), and breast (n=2) cancer were enrolled in this study. Out of those subjects, 18 (78%) completed the study. The authors found that 28% of subjects achieved stable disease, 11% achieved partial response, and 33% achieved complete response. In addition, the results showed higher numbers of chemotherapy cycles (p=0.015) and number of hyperthermia sessions (p<0.001) performed were associated with a better response. The authors conclude that these results need to be confirmed in larger studies.

In 2017, van der Horst and colleagues conducted a systematic review of the clinical benefit of hyperthermia and/or chemotherapy in subjects with pancreatic cancer. The search yielded 14 studies with 395 subjects. Out of the 395 subjects 248 received regional hyperthermia (n=189), intraoperative hyperthermia (n=39), or whole body hyperthermia (n=20), combined with chemotherapy, radiotherapy, or both. Results showed that overall response rate was better for hyperthermia groups; however, the quality of the studies was low level due to no randomization and some studies being retrospective. The authors concluded that randomized control trials are needed to establish efficacy.

There has also been interest in combining hyperthermia with intravesicular chemotherapy in individuals with bladder cancer. However, published evidence is very limited.

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History

Status	Date	Action
New	05/03/2018	Medical Policy & Technology Assessment Committee (MPTAC) review.
New	05/02/2018	Hematology/Oncology Subcommittee review. Initial document development. Moved content of MED.00026 Hyperthermia for Cancer Therapy to new clinical utilization management guideline document with the same title.