Hyperthermia (therapy for cancer)

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Policy contains: Cancer therapy; hyperthermia.

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Coverage policy

Hyperthermia therapy for cancer is clinically proven and, therefore, medically necessary when any of the following criteria are met:

I. Local/regional external hyperthermia only for superficial hyperthermia when used in combination with radiation therapy for the treatment of patients with any of the following:
   a. Members ≥ 18 years old who have histologic proof of malignancy with measurable disease ≤ 3 cm in thickness from the body surface.
   b. Superficially recurrent uveal melanoma (National Comprehensive Cancer Network, 2019);
   c. Chest wall recurrence of breast cancer (Vernon, 1996; Zagar, 2010; Data, 2016b); or
   d. Recurrent lymph nodes from head and neck cancer (Datta, 2016c).

II. Hyperthermic intraperitoneal chemotherapy when used in combination with cytoreductive surgery for ANY of the following:
   a. Pseudomyxoma peritonei (National Institute for Health and Care Excellence, 2004);
   b. Peritoneal carcinomatosis from gastric or colorectal cancer without distant (i.e. extra-abdominal) metastases (National Comprehensive Cancer Network, 2010);
   c. Malignant peritoneal mesothelioma with metastasis limited to the abdominal cavity (National Cancer Institute, 2019).
Limitations

All other uses of hyperthermia therapy for cancer are not clinically proven, and considered investigational/experimental.

The following forms of hyperthermia have not been medically proven to be effective and are considered investigational/experimental:

a. Interstitial hyperthermia;

b. Regional hyperthermia (as differentiated from regional external hyperthermia);

c. Regional perfusion hyperthermia (please see note below related to requests for intraperitoneal hyperthermic chemotherapy combined with cytoreductive surgery); and

d. Whole body hyperthermia.

Alternative covered services

None.

Background

Hyperthermia (also called thermal therapy or thermotherapy) is a type of cancer treatment in which body tissue is exposed to high temperatures (up to 113°F). Research has shown that high temperatures can damage and kill cancer cells, usually with minimal injury to normal tissues. By killing cancer cells and damaging proteins and structures within cells, hyperthermia may shrink tumors (American Cancer Society, 2016).

Hyperthermia is almost always used with other forms of cancer therapy, such as radiation therapy and chemotherapy. Hyperthermia may make some cancer cells more sensitive to radiation or harm other cancer cells that radiation cannot damage. When hyperthermia and radiation therapy are combined, they are often given within an hour of each other. Hyperthermia can also enhance the effects of certain anticancer drugs.

Numerous clinical trials have studied hyperthermia in combination with radiation therapy and/or chemotherapy. These studies have focused on the treatment of many types of cancers, including sarcoma, melanoma, and cancers of the head and neck, brain, lung, esophagus, breast, bladder, rectum, liver, appendix, cervix, and peritoneal lining (mesothelioma). Several methods of hyperthermia are currently under study, including local, regional, and whole-body hyperthermia:

I. Local hyperthermia refers to heat that is applied to a very small area, such as a tumor (site-specific). Local hyperthermia is limited to solid tumor cancers. The treatment area may be heated externally with high frequency waves aimed at a tumor from a device outside the body; or to achieve internal heating, one of several sterile probes may be used, including thin, heated wires or hollow tubes filled with warm water, implanted microwave antennae, and radiofrequency electrodes. Methods of heat application used in local hyperthermia include microwaves, interstitial radiofrequency, laser and ultrasound. Examples of the types of local hyperthermia (based on the location of heat application and method of heat application used) include:
   - Surface or superficial hyperthermia — specifically treats superficial tumors such as skin cancers and skin metastases.
   - Interstitial hyperthermia — interstitial microwave hyperthermia and Interstitial nd: YAG laser hyperthermia involves the delivery of heat specifically to the tumor tissue (e.g., prostate, rectal tumor).
II. Regional hyperthermia is used for treating specific areas of the patient’s body, such as the pelvis, abdominal cavity or limbs. Regional hyperthermia utilizes multiple microwaves or ultrasound devices or applicators that deliver deep heat treatment that are used to create an increase in temperature of up to 42°C in a reasonably large area around a tumor. Radiation therapy or chemotherapy is then administered. Regional hyperthermia can be further delineated into Regional Perfusion Hyperthermia when the clinical application of heat is through a perfusion method. Examples of Regional Perfusion Hyperthermia include:
   a. Hyperthermic antineoplastic perfusion – simultaneous delivery of an antineoplastic agent by perfusion with the application of hyperthermia.
   b. Hyperthermic isolated limb perfusion.

III. Continuous hyperthermic peritoneal perfusion is a technique used to treat cancers within the peritoneal cavity (the space within the abdomen that contains the intestines, stomach, and liver), including primary peritoneal mesothelioma and stomach cancer. During surgery, heated anticancer drugs flow from a warming device through the peritoneal cavity. The peritoneal cavity temperature reaches 106-108°F.

IV. Whole-body/systemic hyperthermia in which radiant heat is used to induce systemic temperatures of 41 degrees Centigrade. Whole body/systemic hyperthermia is used to treat metastatic cancer that has spread throughout the body. It can be accomplished using warm-water blankets, hot wax, inductive coils (like those in electric blankets), thermal suits or thermal chambers, which are similar to large incubators or by heating blood delivered through a high-flow arteriovenous shunt (extracorporeal whole body hyperthermia). Whole body/systemic hyperthermia is a complex, labor-intensive technique. The patient may require anesthesia and intubation and always requires careful monitoring. Thus, multiple sessions of whole body/systemic hyperthermia may be difficult to accomplish (American Cancer Society, 2016).

Hyperthermia has been shown to potentiate the effect of radiation therapy in the treatment of superficial lesions (less than 3 cm in depth). Clinical experience has largely been limited to treatment of recurrent, metastatic superficial melanomas, chest wall recurrence of breast cancer and cervical lymph node metastases from head and neck cancers. Tumor depth is a critical factor when combining radiation therapy and hyperthermia. Lesions less than 3 cm from the surface treated with radiation therapy and hyperthermia have been shown to have a significantly greater complete response rate compared to the complete response rate of lesions greater than 3 cm deep.

Hyperthermic intraperitoneal chemotherapy, also referred to as intraperitoneal hyperthermic chemotherapy, has been proposed as an alternative for the treatment of cancers within the peritoneal cavity, including primary peritoneal mesothelioma and gastric cancer. The hyperthermic intraperitoneal chemotherapy 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°F. During traditional intraperitoneal chemotherapy, the chemolytic agents may also be infused at the time of surgery or over a course of several days. However these agents are not heated before being infused, which is the main difference between intraperitoneal therapy and hyperthermia intraperitoneal chemotherapy.

The effectiveness of hyperthermia intraperitoneal chemotherapy is based on the achievement of a hyperthermic intracavity temperature. Because various tissue thicknesses are present within the peritoneal cavity, there is a concern that the entire cavity may not be receiving an even exposure to the medication. Side effects of hyperthermia intraperitoneal chemotherapy include blistering, burns, tissue swelling, blood clots, and bleeding, although these are usually temporary (Gonzalez-Moreno, 2010).
Findings

Recommendations for use of hyperthermia for cancer are found in the National Comprehensive Cancer Network guidelines for recurrent breast cancer (in addition to radiation) and malignant mesothelioma (National Comprehensive Cancer Network, 2020). Numerous other National Comprehensive Cancer Network guidelines find that hyperthermia treatments are investigational (advanced cervical cancer, with chemotherapy or radiation, and disseminated carcinomatosis, small bowel/appendiceal cancer treated with chemotherapy). The National Institute for Clinical Excellence has produced a guideline addressing the procedures governing use of hyperthermia therapy for colorectal metastases and peritoneal carcinomatosis (National Institute for Health and Care Excellence, 2013).

A number of systematic reviews and meta-analyses have been conducted to assess the effectiveness of hyperthermia in treating cancer. Some of the more common cancers in these reviews are the following:

- **Cervical cancer.** A Cochrane review (Lutgens, 2010) of six randomized controlled trials found that combining hyperthermia with radiotherapy resulted in a higher response rate, reduced recurrence rate, and longer overall survival than just radiotherapy alone for patients with locally advanced cervical cancer. Six years later, another meta-analysis (Datta, 2016a) of six randomized controlled trials (n=427) duplicated the finding that adding hyperthermia significantly increased complete response and long term loco-regional control. An increase in survival was not statistically significant.

- **Mesothelioma.** A meta-analysis (Helm, 2015) of 20 articles (n=1047) addressing patients with malignant peritoneal mesothelioma and undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy resulted in a one-, three-, and five-year survival rates of 84, 59, and 42%. Authors concluded the combination led to survival for mesothelioma patients that exceeded past rates.

- **Gastric cancer.** Several meta-analyses addressed the impact of hyperthermia (in combination with surgery) for stomach cancer, including:
  - A meta-analysis (Mi, 2013) of 16 randomized controlled trials (n=1906) showed that treating stomach cancer with hyperthermic intraperitoneal chemotherapy in addition to surgery improved survival at one, two, three, and five years after treatment, compared to surgery only. All differences were significant.
  - An analysis (Sun, 2012) of 10 trials (n=1062) documented significantly longer survival for patients who underwent both surgery and hyperthermia, compared to surgical patients with mitomycin C or 5-FU. Peritoneal recurrence rates were lower in the surgery-plus-hyperthermia group.
  - A review (Gill, 2011) of 10 studies (n=441) showed that when stomach cancer patients achieving complete cytoreduction and then given hyperthermia treatment lived a median of 15 months, compared to just three months for those with only basic supportive therapy.
  - A meta-analysis (Desiderio, 2017) of 32 studies (n=2520), 11 randomized, evaluated effects of hyperthermic intraperitoneal chemotherapy. For patients without the presence of peritoneal carcinomatosis, overall survival rates were greater with the procedure than without ($P = .001$) after 3 – 5 years. The chemotherapy group had significantly higher complication rates for both patients with and without peritoneal carcinomatosis.

- **Breast cancer.** A meta-analysis (Datta, 2016b) of 34 studies of women with locoregional recurrent breast cancer (n=2120) demonstrated that a higher complete response rate was achieved with radiation therapy plus hyperthermia, compared to just radiation therapy in two-arm studies (60.2 vs. 38.1%). The complete response rate in one-arm studies reached 63.4%.
• **Ovarian cancer.** A review (Huo, 2015) of 37 studies of women with epithelial ovarian carcinoma who had cytoreductive surgery and chemotherapy compared those with and without additional hyperthermic intraperitoneal chemotherapy. The group with hyperthermia had a significantly greater survival rate at one, two, three, four, five, and eight years after treatment. Another review (Chiva, 2015) of 11 studies (n=248) of advanced ovarian cancer and eight studies (n=499) with recurrent sensitive ovarian cancer were evaluated for survival. Those women with primary ovarian cancer treated with primary debulking and hyperthermia had a median survival of 37.3 months, while the recurrent cohort’s median survival was 36.5 months; the authors conclude there is no advantage of hyperthermia to treating ovarian cancer.

• **Bladder cancer.** A review (Longo, 2016) of 15 studies (n=346) of bladder cancer patients who underwent hyperthermia treatment concluded the treatment can be effective regardless of adjunctive therapies. Another review (Lammers, 2011) of 22 studies of microwave-induced hyperthermia with intravesical chemotherapy for bladder cancer found a 59% lower recurrence rate than those treated with chemotherapy alone, but cautioned against drawing conclusions due to the limited number of randomized trials and heterogeneity in study design.

• **Esophageal cancer.** A meta-analysis (Hu, 2017) of 19 randomized controlled trials (n=1519) analyzed outcomes for esophageal cancer patients who underwent radiation and chemotherapy, and compared those with and without regional hyperthermia. The hyperthermia group had greater survival, complete response, and effective rates after one, three, five, and seven years, along with lower recurrence and distant metastasis rates. This research represented the first systematic review of the effects of hyperthermia on persons with esophageal cancer.

• **Head and neck cancer.** A review (Datta, 2016c) of six articles (n=451), five of which were randomized, showed a complete response of 62.5% for patients with head and neck cancer treated with thermoradiotherapy, compared to 39.6% treated with radiotherapy alone. Again, this was the first systematic review of hyperthermia for this type of cancer.

• **Colorectal cancer.** A Cochrane review (De Haas-Kock, 2009) of six randomized controlled trials (n=520) analyzed differences in outcomes for rectal cancer patients treated with surgery plus hyperthermia compared to those with surgery only. After two years, overall survival was significantly greater in the combination therapy group, but the difference disappeared at the three-, four-, and five-year marks. A statistically significantly higher complete tumor response was reported for the combination therapy group. A study (Esquivel, 2014) of 1,013 colorectal cancer patients with peritoneal carcinomatosis grouped subjects into those who did and did not undergo hyperthermic intraperitoneal chemotherapy. Those who did had a greater median survival (in months) for each severity level; I (86 versus 45); II (43 versus 19); III (29 versus 8); and IV (28 versus 6). A systematic review (Baratti, 2016) of 32 studies that addressed colorectal cancer patients with cytoreductive surgery with hyperthermic intraperitoneal chemotherapy revealed a median overall survival of 31.6 months; major morbidity of 32.6%, and mortality of 2.9%. A systematic review (Lopez-Lopez, 2016) of nine articles determined that hyperthermic intraperitoneal chemotherapy resulted in lower survival rates for elderly patients. A meta-analysis (Shan, 2014) of 15 studies (n=1583) determined that quality of life after surgery and hyperthermic intra-peritoneal chemotherapy for peritoneal carcinomatosis was significantly improved one year after treatment for overall health and emotional health; insignificant improvements were noted for physical health, social health, and functional health.
On March 16, 2020, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “hyperthermia”, “thermotherapy,” and “cancer.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.


**Policy updates**

5/2016: initial review date and clinical policy effective date: 7/2016


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