Hyperthermia (therapy for cancer)

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Policy contains: Cancer therapy; hyperthermia.

This policy is a Sandhills Center Clinical Coverage Policy adopted from AmeriHealth Caritas of North Carolina. These clinical policies are used to assist with making coverage determinations. Sandhills Center's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Sandhills Center when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Sandhills Center clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Sandhills Center's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Sandhills Center will update its clinical policies as necessary. Sandhills Center clinical policies are not guarantees of payment.

Coverage policy

Hyperthermia therapy for cancer is clinically proven and, therefore, medically necessary when used as local therapy in connection with radiation therapy for the treatment of primary or metastatic cutaneous or subcutaneous superficial malignancies, including superficial recurrent melanoma, chest wall recurrence of breast cancer, and cervical lymph node metastases from head and neck cancer (Centers for Medicare & Medicaid Services, 1984).

Limitations

All other uses of hyperthermia therapy for cancer are not clinically proven, and therefore, investigational/experimental, including when used alone or in connection with chemotherapy. Whole body hyperthermia therapy for cancer is not clinically proven, and therefore, not medically necessary (Centers for Medicare & Medicaid Services, 1984).

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 degrees Fahrenheit). 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 in combination 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 administered 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:

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) (American Cancer Society, 2016).

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 degrees Celcius in a reasonably large area around a tumor. Radiation therapy or chemotherapy is then administered. Regional hyperthermia can be further delineated into regional perfusion, which is hyperthermia when the clinical application of heat is through a perfusion method. Examples of regional perfusion hyperthermia include:

- Hyperthermic antineoplastic perfusion – simultaneous delivery of an antineoplastic agent by perfusion with the application of hyperthermia.
- Hyperthermic isolated limb perfusion (American Cancer Society, 2016).

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 degrees Fahrenheit to 108 degrees Fahrenheit (American Cancer Society, 2016).

Whole-body/systemic hyperthermia is a technique in which radiant heat is used to induce systemic temperatures of 41 degrees Celsius. 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 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).

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

Most cancer-specific guidelines on treatment issued by the National Comprehensive Cancer Network do not mention hyperthermia as a therapy, including the guidelines for bladder, breast, cervical, head/neck, and rectal cancer. Limited endorsement of the treatment is included for the following:

- Colon cancer — cytoreductive debulking with hyperthermic intraperitoneal chemotherapy can be considered in experimental centers, even though it has “significant morbidity and mortality.”
- Cutaneous melanoma — chemotherapy under hyperthermic conditions for regionally recurrent cases is possible, as it has showed some efficacy, but also increased toxicity, in studies.
- Gastric cancer — while hyperthermic intraperitoneal chemotherapy may be a therapeutic alternative for carefully selected Stage 4 patients in the setting of clinical trials, the treatment is under further investigation (National Comprehensive Cancer Network, 2021).

The National Institute for Clinical Excellence guideline on use of cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis states the procedure shows “frequent and serious” complications, and recommends caution on its use (National Institute for Health and Care Excellence, 2021). An earlier guideline by the Institute stated that current evidence on safety and efficacy was insufficient to recommend hyperthermia for pseudomyxoma peritonei as standard practice (National Institute for Health and Care Excellence, 2004).

Other guidelines address hyperthermia use for specific cancers. Some recommend the treatment. For example, a French guideline states that hyperthermic intraperitoneal chemotherapy can be proposed following adjuvant chemotherapy by carboplatin and paclitaxel for ovary, fallopian tube, and primary peritoneum cancers (Lavoue, 2019). Others do not recommend hyperthermia. A European Society of Coloproctology guideline concludes that evidence and consensus for the treatment of metastatic colorectal cancer with hyperthermia are lacking (Klaver, 2017).

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:

- **Various cancers (elderly patients).** A systematic review of 13 studies (n = 2,544 patients) determined

that elderly patients undergoing cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy for cancer had significantly elevated rates of 90-day postoperative mortality and 30-day Grade 3 or higher

postoperative morbidity (Gagniere, 2018). A systematic review found that in only two of nine articles were morbidity and mortality significantly different between those treated with hyperthermia and chemotherapy versus controls among elderly cancer patients. Survival rates were consistently lower among elderly versus younger patients (Lopez-Lopez, 2016).

- **Various cancers (clinical trials).** A systematic review of 13 completed and 57 active clinical trials notes that cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy for cancer has suffered from a lack of clinical trials to validate expanding its use. Current studies are attempting to improve patient selection, strategic sequences of treatment, cytoreductive strategies, chemotherapeutics, optimal hyperthermic temperature and timing, and toxicity profiles. (Morano, 2018).

- **Cervical cancer.** Several large reviews address hyperthermia in locally advanced cervical cancer, including:
    - A systematic review/network meta-analysis of 59 studies (n = 9,894) evaluated different treatments in terms of overall survival, acute morbidity, late morbidity, and long-term locoregional control. The three most effective treatments were 1) hyperthermia plus radiation therapy; 2) hyperthermia plus radiation therapy/chemotherapy; and 3) chemotherapy plus radiation therapy (Datta, 2019).
    - A meta-analysis (Datta, 2016a) of six randomized controlled trials (n = 427) duplicated the finding that adding hyperthermia to cervical cancer treatment significantly increased complete response and long-term locoregional control. An increase in survival was not statistically significant.
- **Mesothelioma.** A meta-analysis (Helm, 2015) of 20 articles (n = 1,047) addressing patients with malignant peritoneal mesothelioma and undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy resulted in 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.

- **Pancreatic cancer**. A systematic review of 14 studies (n = 395) with locally advanced and/or metastatic pancreatic cancer, included patients treated with regional (n = 189), intraoperative (n = 39) or whole-body hyperthermia (n = 20), combined with chemotherapy, radiotherapy, or both. Quality of the studies was low. Six studies including a control group showed a longer median overall survival in the hyperthermia groups (11.7 months versus 5.6 months). Overall response rate in three studies with a control group was greater for the hyperthermia groups (43.9% versus 35.3%). The quality of the reviewed studies was limited (van der Horst, 2018)

- **Gastric cancer.** Several meta-analyses addressed the impact of hyperthermia (in combination with surgery) for stomach cancer, including:
    - A systematic review of 15 studies (n = 964) of perforated gastric cancer states that indications for hyperthermic intraperitoneal chemotherapy for the disorder need clarification (Melloni, 2020).
    - A systematic review of prophylactic hyperthermic intraperitoneal chemotherapy for patients with gastric cancer included 22 studies (n = 1,145), only three randomized. Ranges for prophylactic and surgery alone were 17% – 60% and 25% – 43% for morbidity, 32 – 35 and 22 – 28 months for median overall survival, 39% – 87% and 17% – 61% for five-year survival, and 7% – 27% and 14% – 45% for peritoneal recurrence; surgery was slightly better in each. Authors caution

that studies were heterogeneous and outdated, and that new trials are needed (Brenkman, 2019).
    - A meta-analysis of 21 randomized trials (n = 1,674) showed patients treated with hyperthermic intraperitoneal chemotherapy, compared with controls, had significantly higher three-year survival (risk ratio 1.61) and complete response rate (2.35). Authors observed no significant difference in adverse reactions (Liu, 2019).
    - A meta-analysis (Desiderio, 2017) of 32 studies (n = 2,520), 11 randomized, evaluated effects of hyperthermic intraperitoneal chemotherapy on gastric cancer. For patients without the presence of peritoneal carcinomatosis, there was no difference in three-year survival, a median increase of four months after the therapy. The chemotherapy group had significantly higher complication rates for both patients with and without peritoneal carcinomatosis.
- **Recurrent breast cancer.** Large reviews on hyperthermia treatment of recurrent breast cancer include:
    - A systematic review of 22 studies (n = 2,230) found a significant relationship for complete response (10/15 studies), duration of local control (10/13), overall survival (2/2), and thermal toxicity (7/11). Patients who received high thermal dose had an average 34% more complete responses than those who received low thermal dose (Bakker, 2019).
    - A meta-analysis (Datta, 2016b) of 34 studies of women with locoregional recurrent breast cancer (n = 2,120) 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 systematic review of 17 trials (n = 1,464) of hyperthermic intraperitoneal chemotherapy for epithelial ovarian cancer found improved overall and progression-free survival, but no increases in one-year overall and one/two-year progression-free survival. Authors call for more studies, and describe the treatment for ovarian cancer as “still controversial” (Wu, 2019).
    - A systematic review/meta-analysis of 15 studies (two randomized) of hyperthermic intraperitoneal chemotherapy for ovarian cancer improved disease-free survival (hazard ratio .603) and overall survival (.640). In cases of recurrent disease, the treatment was associated with better overall survival, but not with disease-free survival (Kim, 2019).
    - A meta-analysis of 13 studies of hyperthermic intraperitoneal chemotherapy for ovarian cancer showed improved overall progression-free survival for advanced primary ovarian cancers, but not for progression-free survival in recurrent ovarian cancer (Zhang, 2019).
- **Bladder cancer.** Several large reviews of hyperthermia treatment of bladder cancer include:
    - A meta-analysis of adverse events and recurrence rate of non-muscle invasive bladder cancer compared thermal intravesical chemotherapy versus normal temperature intravesical chemotherapy. It included 12 studies (11 randomized), n = 888 patients. The hyperthermia group had lower disease recurrence at 24 months ($P < .00001$) and 36 months ($P = .0002$), with no difference in adverse events rate ($P = .67$) (Liu, 2019).
    - 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.

- **Esophageal cancer.** A meta-analysis (Hu, 2017) of 19 randomized controlled trials (n = 1,519) 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, copared to 39.6% treated with radiotherapy alone. Again, this was the first systematic review of hyperthermia for this type of cancer.

- **Colorectal cancer.** Several large reviews addressed hyperthermia treatment for colorectal cancer, including:
    - A systematic review of highly selected patients, oxaliplatin hyperthermic intraperitoneal chemotherapy cisplatin with mitomycin C in metastatic colorectal cancer had "unusual prolonged survival" (median 60 months), and major complications in less than 30% of patients, with limited hematological toxicity. Authors describe the study as an "interesting protocol," after the failed trial PRODIGE 7 of oxaliplatin hyperthermic intraperitoneal chemotherapy (Pinto, 2019).
    - A systematic review and meta-analysis of nine articles (n = 1,308) of colorectal cancer with peritoneal metastasis treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy revealed overall and disease-free survival in colon tumors is significantly lower than in rectal tumors. Most studies were heterogenous (Tonello, 2019).
    - A systematic review of 16 studies of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal peritoneal metastases found no strong evidence for the efficacy of neoadjuvant chemotherapy, and limited evidence for adjuvant chemotherapy (Waite, 2017).
    - A systematic review of 28 studies documented a recurrence rate ranging (by study) from 22.5% to 82%, after treatment for peritoneal carcinomatosis of colorectal origin by cytoreductive surgery and intraperitoneal chemotherapy. Median time to recurrence varied from nine to 23 months. Authors describe this recurrence as "very common" (van Oudheusden, 2015).

References

On March 4, 2021, 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.

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Policy updates

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