Clinical Policy Title: Hyperthermia (therapy for cancer)

Clinical Policy Number: 05.02.09

Effective Date: July 1, 2016
Initial Review Date: May 18, 2016
Most Recent Review Date: May 1, 2018
Next Review Date: May 2019

Related policies:

Various cancer treatment policies.

ABOUT THIS POLICY: Select Health of South Carolina has developed clinical policies to assist with making coverage determinations. Select Health of South Carolina’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 Select Health of South Carolina 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. Select Health of South Carolina’s 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. Select Health of South Carolina’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Select Health of South Carolina will update its clinical policies as necessary. Select Health of South Carolina’s clinical policies are not guarantees of payment.

Coverage policy

Select Health of South Carolina considers the use of hyperthermia therapy for cancer to be 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 melanoma (NCCN, 2013);
   c. Chest wall recurrence of breast cancer (NCCN, 2009b); or
   d. Recurrent lymph nodes from head and neck cancer (Emami, 1996).

II. Hyperthermic intraperitoneal chemotherapy when used in combination with cytoreductive surgery for ANY of the following:
   a. Pseudomyxoma peritonei (NICE, 2004);
   b. Peritoneal carcinomatosis from gastric or colorectal cancer without distant (i.e. extra-abdominal) metastases (NCCN, 2011);
c. Malignant peritoneal mesothelioma with metastasis limited to the abdominal cavity (NCI, 2009).

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 (ACS, 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 (ACS, 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).

**Searches**

Select Health of South Carolina searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on March 12, 2018. Search terms were: “hyperthermia”, “thermotherapy,” and “cancer.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.
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 (NCCN, 2009). 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). Others make no mention of hyperthermia treatments for non-small cell lung cancer, gastric cancer, pancreatic cancer, advanced colon cancer, hepatobiliary cancer, and thymus cancer. The National Institute for Clinical Excellence has produced a guideline addressing the procedures governing use of hyperthermia therapy for colorectal metastases and peritoneal carcinomatosis (NICE, 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 of six randomized controlled trials (RCTs) 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 (Lutgens, 2010). Six years later, another meta-analysis of six RCTs (n=427) duplicated the finding that adding hyperthermia significantly increased complete response and long term loco-regional control, plus a non-significant increase in survival (Datta, 2016a).

- **Mesothelioma.** A meta-analysis 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 percent. Authors concluded the combination led to survival for mesothelioma patients that exceeded past rates (Helm, 2015).

- **Gastric cancer.** Several meta-analyses addressed the impact of hyperthermia (in combination with surgery) for stomach cancer, including:
  - A meta-analysis of 16 RCTs (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 (Mi, 2013).
  - An analysis 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 (Sun, 2012).
  - A review 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 (Gill,
A meta-analysis 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 (Desiderio, 2017).

- **Breast cancer.** A meta-analysis 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 percent). The complete response rate in one-arm studies reached 63.4 percent (Datta, 2016b).

- **Ovarian cancer.** A review 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 (Huo, 2015). Another review 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 (Chiva, 2015).

- **Bladder cancer.** A review of 15 studies (n=346) of bladder cancer patients who underwent hyperthermia treatment concluded the treatment can be effective regardless of adjunctive therapies (Longo, 2016). Another review of 22 studies of microwave-induced hyperthermia with intravesical chemotherapy for bladder cancer found a 59 percent 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 (Lammers, 2011).

- **Esophageal cancer.** A meta-analysis of 19 RCTs (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 (Hu, 2017).

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

**Colorectal cancer.** A Cochrane review of six RCTs (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 significantly higher complete tumor response was reported for the combination therapy group (De Haas-Kock, 2009). A study 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) (Esquivel, 2014). A systematic review 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 percent, and mortality of 2.9 percent (Baratti, 2016).

A systematic review of nine articles determined that hyperthermic intraperitoneal chemotherapy resulted in lower survival rates for elderly patients (Lopez-Lopez, 2016).

A meta-analysis 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 (Shan, 2014).

Policy changes:

A total of two guidelines/other and seven peer-reviewed references were added to this policy in March 2018.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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</thead>
<tbody>
<tr>
<td>Desiderio (2017)</td>
<td>Key points:</td>
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</tbody>
</table>
| Effects of hyperthermic intraperitoneal chemotherapy in advanced gastric cancer | - Meta-analysis of 32 studies (n=2520), 11 randomized, persons with advanced gastric cancer.  
- Effects of hyperthermic intraperitoneal chemotherapy, for patients with and without peritoneal carcinomatosis.  
- In patients without peritoneal carcinomatosis, overall survival rates were greater with the procedure than without (p=.001) after 3 – 5 years.  
- In patients with peritoneal carcinomatosis, median survival at 4 months was higher (p<.001) but there was no difference in the 3-year overall survival (p = 0.85).  
- A significantly elevated risk of complications was observed for both patients with (RR = 2.15, P < 0.01) and without (RR = 2.17, P < 0.01) the procedure. |
<p>| Datta (2016a)       | Key points:                       |
| Hyperthermia in locally | - Meta-analysis of 6 RCTs (n=427). |</p>
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<tr>
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| advanced cervical cancer | - Cervical cancer patients given radiotherapy with vs. without loco-regional hyperthermia.  
- Group with hyperthermia had a non-significant survival advantage of 8.4%, no difference in acute or late toxicities.  
- One study showed a significantly higher complete response rate for hyperthermia group (83.3% vs. 46.7%).  
- Hyperthermia for cervical cancer seems promising, but needs further confirmation. |
| Datta (2016b) | **Key points:**  
- Meta-analysis of 26 single-arm (n=1483) and 8 two-arm studies (n=627).  
- Comparisons of breast cancer patients given radiation therapy with vs. without hyperthermia.  
- In the two-arm studies, complete response achieved in 60.2% of hyperthermia cases, vs. 38.1% given radiation alone.  
- In the single-arm studies, complete response achieved in 63.4% of cases.  
- Combining hyperthermia and re-irradiation achieved a complete response of 66.6%. |
| Helm (2015) | **Key points:**  
- Meta-analysis of 20 articles (n=1047) of patients with malignant peritoneal mesothelioma.  
- Patients underwent cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC).  
- Survival at 1, 3, and 5 years after treatment was 84%, 59%, and 42%, which are higher than historic data without HIPEC. |
| Shan (2014) | **Key points:**  
- Systematic review of 15 studies (n=1583) measured for quality of life changes one year after cytoreductive surgery and HIPEC for various cancers.  
- Overall health status and emotional health status significantly higher after one year.  
- Physical health, social health, and functional health improved, but not significantly. |
| Mi (2013) | **Key points:**  
- Meta-analysis of 16 RCTs (n=1906), persons with advanced gastric cancer.  
- Comparison of survival rates of surgery plus HIPEC, vs. surgery alone.  
- Combination group had significantly higher survival at 1, 2, 3, 5, and 9 years.  
- Hyperthermia not associated with higher risk of anastomotic leakage, ileus, bowel perforation, myelosuppression, gastrointestinal reaction, and hypohepatia, but was associated with increased incidence of abdominal pain. |

**References**

**Professional society guidelines/other:**


Peer-reviewed references:


Overgaard J, Gonzalez Gonzalez D, Hulshof MC, et al. Randomised trial of hyperthermia as adjuvant to


**CMS National Coverage Determinations (NCDs):**


[https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=66&ncdver=1&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=hyperthermia&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAAACAAAAAAA%3d%3d&](https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=66&ncdver=1&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWord=hyperthermia&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAAACAAAAAAA%3d%3d&). Accessed March 12, 2018.

**Local Coverage Determinations (LCDs):**

No LCDs identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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<thead>
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<td>C45.1</td>
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