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 18, 2016
Next Review Date: May 2017

Related policies:
None.

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

Coverage policy

Keystone First considers the use of hyperthermia therapy for cancer to be clinically proven and, therefore, medically necessary when 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 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;
   c. Chest wall recurrence of breast cancer; or
   d. Recurrent lymph nodes from head and neck cancer.

II. Hyperthermic intraperitoneal chemotherapy (HIPEC) is medically necessary when used in combination with cytoreductive surgery for ANY of the following:
   a. Pseudomyxoma peritonei (PMP)
   b. Peritoneal carcinomatosis from gastric or colorectal cancer without distant (i.e. extra-abdominal) metastases
   c. Malignant peritoneal mesothelioma with metastasis limited to the abdominal cavity
Limitations:

All other uses of hyperthermia therapy for cancer are not medically necessary.

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

Note: Requests for intraperitoneal hyperthermic chemotherapy combined with cytoreductive surgery should be reviewed for medical necessity as an inpatient surgical procedure using nationally recognized InterQual standards.

NOTE: The following codes are not included in the Medicaid medical fee schedule in Pennsylvania

77605 - Hyperthermia externally generated; deep (ie, heating to depths greater than 4 cm)

77620 - Hyperthermia generated by intracavitary probe(s)

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.

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). Many of these studies, but not all, have shown a significant reduction in tumor size when hyperthermia is combined with other treatments. However, not all of these studies have shown increased survival in patients receiving the combined treatments.

Several methods of hyperthermia are currently under study, including local, regional, and whole-body hyperthermia:
I. Local Hyperthermia (LHT) refers to heat that is applied to a very small area, such as a tumor (site-specific). LHT 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; and
- 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 (RHT) is used for treating specific areas of the patient’s body, such as the pelvis, abdominal cavity or limbs. RHT 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; and
   b. Hyperthermic Isolated Limb Perfusion.

III. Continuous hyperthermic peritoneal perfusion (CHPP) 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 (WBH) in which radiant heat is used to induce systemic temperatures of 41 degrees Centigrade. WBH 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). WBH is a complex, labor-intensive technique. The patient may require anesthesia and intubation and always requires careful monitoring. Thus, multiple sessions of WBH may be difficult to accomplish.

V. 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. 77600 Hyperthermia, externally generated; superficial (i.e., heating to a depth of 4 cm or less)
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°F. During traditional intraperitoneal chemotherapy (IPC), 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 IPC and HIPEC. The effectiveness of HIPEC 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 HIPEC include blistering, burns, tissue swelling, blood clots, and bleeding, although these are usually temporary.

The occurrence of mesotheliomas has recently increased, with this increase being associated to asbestos exposure. Survival rates for patients who are diagnosed with Peritoneal Carcinomatosis (PC) are poor, with a median survival time being reported as 12–25 months (Efiom-Ekahn, 2003). Specific to malignant peritoneal mesothelioma, a median survival of approximately 12 months has been reported after treatment with standard therapies such as palliative surgery, systemic/intraperitoneal chemotherapy, and abdominal irradiation (Baratti, et al., 2011).

The Food and Drug Administration (FDA) has approved hyperthermia for use in the treatment of cancer when combined with radiation therapy for the palliative management of certain solid surface and subsurface malignant tumors that are progressive or recurrent despite conventional therapy. The BSD-500 device (BSD Medical Corporation) has FDA clearance for superficial heating (less than a 4 cm depth). Substantial clinical data exist demonstrating the efficacy of combined radiation and hyperthermia in the treatment of superficial tumors. The complete response rate of combined therapy has been reported at approximately 70%, compared to a response rate of 35% for radiotherapy alone. Toxicity (principally, thermal burns and blisters) is generally low (approximately 10%) and not treatment-limiting. Studies investigating the clinical application of whole body, interstitial and regional hyperthermia combined with conventional treatment modalities (radiation, chemotherapy) in the treatment of multiple malignant diseases are numerous, but the studies have a small number of patients, lack standardized technique, are not randomized or controlled and lack long-term outcomes.

**Searches**

Keystone First 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 April 4, 2016. Search terms were: “Extracorporeal whole body hyperthermia”, “Intraperitoneal hyperthermic perfusion”, (local hyperthermia”, “regional hyperthermia”, “regional perfusion hyperthermia”, “whole body hyperthermia.” “MESH”.

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

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.

However, not all randomized studies have been positive. RTOG conducted the first randomized study of radiation and HT versus radiation alone in superficial tumors (RTOG 8104). The study population was patients with primarily chest wall recurrences of breast cancer and head and neck cancers. The CR rate was approximately 30% in both arms. In the subset of tumors less than 3 cm, a better CR rate was noted with radiation and heat (62%) than with radiation alone (40%). However, only 56% of the tumors less than 3 cm and 36% of the lesions ≥ 3 cm received adequate HT. It was postulated that the higher response rate in patients with smaller lesions was related to the fact that a larger proportion of the smaller tumors received an adequate thermal dose. Two other negative randomized trials of superficial tumors tested the difference between the number of HT treatments and did not prospectively control for cumulative thermal dose.

Positive results for the addition of HT were obtained for the combined meta-analysis of five randomized controlled trials with individual patient data for measurable breast cancer lesions for which local therapy was indicated and surgery was not feasible. Among the five studies, a total of 171 patients were randomly assigned to radiotherapy alone versus radiation therapy with HT.

### Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
<th>Key points:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang C-Q, et al. (2014) Cytoreductive Surgery (CRS) plus Hyperthermic Intraperitoneal Chemotherapy Improves Survival for Patients with Peritoneal Carcinomatosis (PC) from Colorectal Cancer (CRC)</td>
<td><strong>Key points:</strong></td>
<td></td>
</tr>
<tr>
<td>Falk MH, et al (2002) Overview of clinical application of hyperthermia</td>
<td><strong>Key points:</strong></td>
<td></td>
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</table>

- The clinical application of hyperthermia with increase of tissue temperatures (range 40-
44°C has been integrated in multimodal anti-cancer strategies. Phase I or II (n = 17) and phase III trials (n = 16) investigating the effect of hyperthermia combined with radiotherapy (n = 10 trials), chemotherapy (n = 15 trials), or both (n = 8 trials) in a total of more than 2200 patients.

- The trials were performed in a variety of solid tumours (e.g. melanoma, head and neck cancer, breast cancer, cancer of the gastrointestinal or urogenital tract, glioblastoma, sarcoma) in paediatric or adult patients.
- Profound research has produced a scientific basis for the simultaneous application of hyperthermia in combination with ionizing radiation and/or systemic chemotherapy.
- Hyperthermia is becoming more accepted clinically, due to the substantial technical improvements made in achieving selected increase of temperatures in superficial and deep-seated tumours.
- The combination of hyperthermia and chemotherapy or radiochemotherapy is further tested within clinical protocols (phase II/III) in order to improve local tumour control and relapse-free survival in patients with high-risk or advanced tumours of different entities.

**Key points:**

- A cohort of patients (n=55) with peritoneal surface disease from colorectal cancer who received CS and HIPEC. Follow-up occurred one month post-procedure and every six months thereafter up to five years.
- The median follow-up period was 86 months. The five-year overall survival rate for this cohort of patients with resection status of R 0 or R1 was 36% and 14% respectively. The overall postoperative morbidity and mortality was 41.8% and 5.5% respectively.
Baratti et al. (2013)  
Results of a case series (n=108) of diffuse malignant peritoneal mesothelioma (DMPM)

Key points:
- A case series (n=108) of diffuse malignant peritoneal mesothelioma (DMPM) patients undergoing complete cytoreduction and closed-abdomen HIPEC with cisplatin and doxorubicin or mitomycin-C.
- Eligibility criteria for combined treatment included histological diagnosis of DMPM, age < 7, no significant comorbidities or extraperitoneal metastases and peritoneal disease amenable to potentially complete cytoreduction.
- Primary study end-points were overall survival (OS) and progression-free survival (PFS). OS and PFS were dated from the day of cytoreduction with HIPEC to the date of death for any cause or first recurrence, respectively. A total of 49 patients received systemic chemotherapy preoperatively.
- In the overall series, median estimated follow-up was 48.8 months (95% confidence interval (CI) = 37.1–60.6).

Perez CA et al (1991)  
Randomized phase III study comparing irradiation and hyperthermia with irradiation alone in superficial measurable tumors. Final report by the Radiation Therapy Oncology Group.

- A total of 307 patients with superficial measurable tumors were registered on a Radiation Therapy Oncology Group (RTOG) protocol involving fractionated radiation therapy, either alone or followed immediately by hyperthermia (42.5 degrees C, 45-60 min).
- Overall complete response (CR) was observed in 30% of the lesions treated with radiotherapy (RT) and 32% of those receiving RT and heat. Response was found to be significantly related to both maximum tumor diameter (less than 3 or greater than or equal to 3 cm) and site/histology (breast/adenocarcinoma, head and neck/squamous, or other site/histologies).
- In tumors less than 3 cm in diameter in the breast, trunk, and extremities, a better CR rate was noted with irradiation and heat (52 and 67%) than with irradiation alone (40 and 0%).
- However, in the head and neck there was only minimal difference in CR with irradiation alone or combined with hyperthermia (50 vs 38%). In lesions less than 3 cm treated with irradiation and heat, there was improved local control. In lesions greater than 3 cm, there was no difference in local control between the two treatment arms.
- The higher response rate in patients with smaller lesions (less than 3 cm) may be explained by the fact that these tumors are easier to heat. Problems in correlating tumor response with quality of heating include less than optimal heating in larger lesions and the limited ability of current thermometry to map the temperature distribution in a tumor. Acute and late toxicities in both treatment arms were comparable, except for an overall 30% incidence of thermal blisters in the heated tumors.

Glossary

Nd:YAG (neodymium-doped yttrium aluminium garnet; Nd:Y3Al5O12) — Is a crystal that is used as a lasing medium for solid-state lasers. The dopant, triply ionized neodymium, Nd (III), typically replaces a small fraction (1%) of the yttrium ions in the host crystal structure of the yttrium aluminium garnet (YAG), since the two ions are of similar size. It is the neodymium ion which provides the lasing activity in the crystal, in the same fashion as red chromium ion in ruby lasers.

Sarcoma— A type of cancer that develops from certain tissues, like bone or muscle. Bone and soft tissue sarcomas are the main types of sarcoma. Soft tissue sarcomas can develop from soft tissues like fat, muscle, nerves, fibrous tissues, blood vessels, or deep skin tissues. They can be found in any part of the body.

References

Professional society guidelines/other:
Peer-reviewed references:


Clinical trials:

Searched clinicaltrials.gov on April 5, 2016 using terms hyperthermia, regional local and whole body, cancer treatments, chemotherapy “ | Open Studies. 172 studies found, 169 relevant.


Others can be found at: https://clinicaltrials.gov/ct2/results?term=hyperthermia+for+cancer&recr=Open&no_unk=Y.

CMS National Coverage Determinations (NCDs):


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.

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Comments</th>
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<tbody>
<tr>
<td>77600</td>
<td>Hyperthermia, externally generated; superficial (i.e., heating to a depth of 4 cm or less)</td>
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<tr>
<td>77620</td>
<td>Hyperthermia generated by intracavitary probe(s)</td>
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<tr>
<td>96446</td>
<td>Chemotherapy administration into the peritoneal cavity via indwelling port or catheter</td>
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<tr>
<th>ICD-10 Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>C18.1</td>
<td>Malignant neoplasm of appendix [without pseudomyxoma]</td>
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<tr>
<td>C43.0 - C44.9</td>
<td>Malignant melanoma of skin</td>
<td></td>
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<tr>
<td>C45.1</td>
<td>Mesothelioma of peritoneum</td>
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<td>C50.011 - C50.929</td>
<td>Malignant neoplasm of breast</td>
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<tr>
<td>C76.0</td>
<td>Malignant neoplasm of head, face, and neck</td>
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<tr>
<td>C77.0</td>
<td>Secondary and unspecified malignant neoplasm of lymph nodes of head, face, and neck</td>
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<tr>
<td>C78.6</td>
<td>Secondary malignant neoplasm of retroperitoneum and peritoneum [pseudomyxoma peritonei]</td>
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<tr>
<td>D03.0 - D03.9</td>
<td>Melanoma in situ</td>
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