

# Hyperthermia: How Can It Be Used?

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## ABSTRACT

Hyperthermia (HT) is a method used to treat tumors by increasing the temperature of the cells. The treatment can be applied in combination with other verified cancer treatments using several different procedures. We sought to present an overview of the different HT tumor treatment, recent advances in the field, and combinational treatment sequences and outcomes. We used a computer-aided search to identify articles that contained the keywords hyperthermia, cancer treatment, chemotherapy, radiotherapy, nanoparticle, and cisplatin. There are three types of HT treatment, which each need the use of applicators that are in contact with or in the proximity of the patient for the purpose of heating. Heating can be achieved using different types of energy (including microwaves, radio waves, and ultrasound). However, the source of energy will depend on the cancer type and location. The temperature used will also vary. HT is rarely used alone, and can be combined with other cancer treatments. When used in combination with other treatments, improved survival rates have been observed. However, despite *in vitro* and *in vivo* studies that support the use of concurrent hypothermia treatments, contradictory results suggest there is a need for more studies to identify other hidden effects of HT.

Hyperthermia (HT) is a type of cancer treatment along with surgery, radiotherapy, chemotherapy, and gene and immunotherapy.<sup>1</sup> In oncology, HT uses an external heat source to increase tissue temperature and kill cancer cells or impede their further growth.<sup>2</sup>

The term 'hyperthermia' applies to several heat application techniques that are implemented in addition to other cancer treatments (particularly chemotherapy and radiotherapy).<sup>3</sup>

High temperatures, as most studies revealed,<sup>4</sup> cause direct injury to cancerous cells and sensitize the cells to other treatment modalities, and augments radiation and chemotherapy with insignificant or no injury to normal tissues.<sup>5</sup> Hence, HT is generally used as an adjuvant treatment for cancer.<sup>6,7</sup>

HT treatment temperatures range between 40–48 °C and the temperature is maintained at a treated site for one hour or more.<sup>6</sup> Because of the consequences high temperature may have on tissues, one can refer to use temperatures >50 °C as coagulation, 60–90 °C as thermal ablation, and >200 °C as charring.<sup>5</sup> Ablation or high-temperature HT is defined as the direct implementation of chemical or

thermal therapies to a tumor to reach annihilation or significant tumor destruction.<sup>8</sup>

The curative capacities, treatment outlay, technical problems, and evidence of efficacy vary depending on the HT approach.<sup>9</sup> While treatment of tumors with HT has been applied since the time of the ancient Greeks, use of this technique has been opposed due to limitations. These include failure to heat the target without damaging the nearby cells, difficulty achieving homogenous heat dispersion throughout the tumor, and inherent problems with targeting invisible micrometastases.

In recent years, advances in nanoparticle-aided thermal therapy hold the ability to overcome most of these problems, but there are still concerns about the use of nanoparticles. While it was known that normal tissues exhibit enhanced thermotolerance toward cancer cells,<sup>9,10</sup> the mechanisms controlling this are largely unknown.<sup>11</sup> Depending on the site of the tumor (e.g., superficial or deep-seated) different treatment modalities can be adopted.

In this review, we present an overview of tumor HT therapy modalities, recent advances in the field, and combinational treatment sequences and outcomes.

### **Treatment Methods**

There are three main clinical methods of high-temperature applications, which depend on the organ to be targeted, the stage of cancer, and the energy distribution technique. Local, regional, and whole-body HT distribute heat to localized, progressive or deep-seated and dispersed malignancies, respectively.<sup>12</sup>

#### **Local hyperthermia**

Local HT is devoted to relatively small tumors ( $\leq 3$  cm up to 5–6 cm),<sup>6,13</sup> located superficially or within an available body cavity such as the rectum or esophagus. In local HT, superficial, intraluminal applicators can be applied and, most frequently, microwaves, radio waves, or ultrasound are used to convey heat to the tumors.<sup>9</sup>

Superficial applicators of different shapes and types (e.g., waveguide, spiral, and current sheet) are positioned on the surface of superficial tumors with a contacting layer called a bolus. To inhibit any side effects, water boluses are concurrently used to keep the temperature of the skin at about 37 °C. These boluses also confirm the electromagnetic linking from the applicator to the tissue. To record the temperature, small thermometers are inserted into tubes or needles attached to the anesthetized tumor tissue.<sup>4</sup>

Cancers located near body cavities, for example in the prostate, rectum, vagina, cervix, or esophagus, can be treated via intracavitary or intraluminal methods, bringing heat directly into these regions. The method for heating superficial tumors is devoted to the spectrum of tumors able to be treated with brachytherapy (head and neck tumors, prostate cancer, brain malignancies, and breast cancer). Compared to brachytherapy, interstitial HT is an invasive procedure and is appropriate for lesions no more than 5 cm in size. This method requires an array of applicators to be fixed under local or, occasionally, general anesthesia.<sup>7</sup>

#### **Regional hyperthermia**

In the regional perfusion HT procedure, part of the patient's blood is removed, heated, and then pumped back into the limb or organ, typically along with anticancer drugs.

Hyperthermic intraperitoneal chemotherapy (HIPEC), has been recommended to treat cancers within the peritoneal cavity, such as primary

peritoneal mesothelioma and gastric cancer. In this method, the heated chemotherapeutic agent is inserted into the peritoneal cavity, increasing the tissue temperature inside the cavity to 41–42 °C.<sup>14</sup>

Regional or partial HT is a method for heating large parts of the body. It is usually used to treat advanced tumors located in the pelvis, abdomen, or thighs. Three key methods can be described: intrinsic (tumors heated with peripheral applicators), thermal (organs or limbs heated with thermal perfusion), and constant hyperthermic peritoneal perfusion (CHPP).

Some of the most useful external applicators for regional HT contain coherent arrays of dipole antenna couples placed in a loop design around the patient. The antennas produce microwave or radiofrequency energy to be absorbed in the target tissue. With such apparatus, target tissue can be heated to 41–42 °C.<sup>15</sup> Malignancies disturbing arms or legs (e.g., melanoma) or other organs (e.g., liver, lung) can be cured with regional HT. This technique, compared to whole body HT, presents fewer systemic side effects.<sup>6</sup>

However, regional HT is more complicated than local heating, mainly because of widespread differences in the physical and physiological properties of different tissues. It needs more refined planning, temperature measuring, and quality assurance. That said, the use of nontoxic and efficient regional HT was approved in phase III studies using slightly invasive thermometry catheters and no significant side effects.<sup>16</sup>

The lack of consistent temperature measurement approaches makes heating upper abdominal tumors difficult. Regional HT of other anatomical areas such as the thorax or neck exposes likely problems and is not possible. Most clinical trials on regional HT have applied the method in combination with radiotherapy.<sup>17</sup>

The Duke Medical Center, in Durham, North Carolina, examined the use of preoperative radiotherapy in adjunct to regional HT.<sup>18</sup> A simple heat therapy is the treatment of pains, tensions, and injuries via implementation of temperatures less than 41 °C for about an hour using physiological processes for elevating metabolic rates and blood flow.<sup>19</sup>

Tumor cell properties, such as hypoxia, poor nutrition, and low pH, can be helpful in heat therapy. The acidic environment of tumor confers resistance to radiation but favors cell death due to

heat. The effect of HT depends on the exposure time and temperature. HT is considered to influence tumor sensitivity to other treatments principally by microenvironmental factors like pH. One hypothesis about the mechanism of HT is that tumor resistant areas are eradicated under hyperthermic situations due to related hypervascularization, which arises at higher temperatures and higher sensitivity because of hypoxia.<sup>20</sup>

### **Whole body hyperthermia**

Whole body hyperthermia (WBH) uses either radiation heat or extracorporeal technologies to raise the temperature of the whole body to at least 41 °C. The typical method used for WBH is immersion in a hot water bath and radiant heat with ultraviolet radiation. In radiant WBH, heat is superficially applied to the whole body using hot blankets, inductive loops, or thermal chambers.<sup>6,18,21,22</sup>

Extracorporeal WBH is obtained by extraction of extracorporeally heated blood. A circuit of blood is shaped beside the body forming an extracorporeal ring. The circulating blood is crossed through a water bath or hot air to heat it and then infused into the main vein. The anticipated body temperature is adjusted and measured by altering the current volume of the warmed injected blood.<sup>23</sup>

Depending on the type of WBH, patients may request general anesthesia or deep sedation during treatment. Heating the body up to 42.0 °C for 60 minutes (dangerous WBH) or 39.5–41.0 °C for three to four hours (modest WBH) may otherwise become difficult.<sup>6,18,21,22</sup> A WBH treatment session usually continues for four hours. It takes two hours to reach the target temperature, which is maintained for a further one hour and is followed by a one hour cooling period. To preserve the patient's systolic blood pressure above 100 mmHg, normal saline is injected. The patient is then checked weekly for problems.<sup>23,24</sup>

While WBH can present the most homogeneous thermal supply, this is associated with the highest chance of difficulties (e.g., thermal pressure in the heart, lungs, liver or brain). Diarrhea, nausea, and vomiting are frequently seen, but they are temporary side effects.<sup>7</sup>

In carcinomas with distant metastases, a fixed maximum temperatures of 42 °C can be preserved for one hour with minor adverse results. Such a procedure can be achieved only in deep numbness

and calm, or general anesthesia. Whether intubation is essential for safe administration is still under debate.<sup>25</sup>

### **Thermal dose and thermal isoeffect dose**

Nowadays cumulative equivalent minutes at a normal targeted treatment temperature of 43 °C achieved within 90% of the tumor volume (CEM43T90) seems to be the most useful dosimetric factor in clinical studies.<sup>26</sup> A thermal dose of 10 CEM43T90 is proposed as a goal of action. By heating a specific tumor to at least 43 °C in 90% of its volume for a cumulative time of 10 minutes or more, there is a doubling of the response and period of answer to HT and radiotherapy versus radiotherapy alone.<sup>27</sup> Simply, the higher the smallest temperatures obtained in the tumor, the better the clinical response.<sup>28</sup>

Radiation Therapy Oncology Group (RTOG) guidelines give instructions for thermometry, which are essential for CEM calculations and declaration of hyperthermia quality.<sup>29</sup> Thermometry in tumors is invasive and thus associated with some specific problems. Some current studies are looking to evolve magnetic resonance imaging (MRI) as an apparatus for non-invasive thermometry.<sup>30</sup>

The thermal isoeffect dose (TID) is frequently used in clinical studies to compare HT exposures with each other. The TID modifies a given thermal dose into CEM43. A 1 °C temperature decrease in the temperature range between 42.5 °C and 47 °C can be rewarded by doubling the description time ( $R = 2$ ) while at less than 42.5 °C the heat exposure has to be elongated even more ( $R = 4$ ).<sup>31</sup>

### **Instruments used in hyperthermia treatments**

Microwaves (433 to 2450 MHz), radio waves (100 KHz to 150 MHz), ultrasound, hot water perfusion (e.g., the use of tubes and blankets), resisting wire embeds, ferromagnetic seeds, nanoparticles, and infrared radiators are used to apply heat to tumors.<sup>32</sup>

Two kinds of probes are used in HT. One to transmit energy to the tissue, an applicator, and another to screen the tissue temperature. Every applicator contains a bolus on the patient's skin. At the time of treatment, this bolus is filled with flowing water that can be heated as required. The bolus helps to physically connect the electromagnetic waves to the patient's body, and decrease the reflection and loss of energy. Heat can then be applied with interstitial and intracavitary probes or external antennas.

Radio frequency at 8–12 MHz is beneficial for heating deep-seated tumors whereas microwave heating at 434–915 MHz is beneficial for superficial tumors. Heating with ultrasound is also possible. Mechanical ultrasonic waves (at 0.2–5 MHz) can efficiently heat a small volume at different depths. Unlike ultrasound imaging, using ultrasonic waves as a heating source has not been utilized clinically.<sup>33</sup>

In most clinical HT systems, a target volume of tissue is exposed to electromagnetic or ultrasound waves. A structure is needed to transfer energy to the tissue and get the best estimate of the area to be treated by the 3D distribution of the specific absorption rate (SAR). Most HT treatments are implemented using external devices (applicators) that deliver energy transfer to the tissue.<sup>34</sup>

The efficiency of HT is related to the temperature achieved during the treatment, as well as the length of treatment and tissue features. To confirm that the required temperature is obtained, but not surpassed, the temperature of the tumor and adjacent tissues is checked during the procedure.

Another challenge of HT is to minimize the damage to healthy tissue. To do this, the aim is to preserve local temperatures under 44 °C and to preserve the whole body temperature under 42 °C, which is the maximum temperature the human body can tolerate.

Recent research has emphasized the importance of exact positioning of heat-delivery devices using ultrasound or MRI, as well as improving new types of nanoparticles that are used as absorbers proposing little or no concerns about toxicity to nearby tissues.<sup>2</sup>

### *Using magnetic nanoparticles to increase treatment effects*

Metastatic and locally advanced disease stages are not suitable for surgical resection, and most of the patients who undergo surgery relapse.<sup>35</sup> A new approach to thermal treatment uses magnetic nanoparticles (MNP) in combination with heat. In this technique, iron oxide nanoparticles are infused into the target tissue, and a magnetic field is used for heating. This offers a chance to heat tumors located in deep body sections like skull (to treat frequent glioblastoma) or the pelvis (for treating prostate and cervical carcinoma).<sup>32</sup>

Homogenous delivery of heat depends on various factors such as the tumor size and depth.<sup>36</sup> The development of this method may overcome the prior

restrictions related to older HT techniques, like the inability to target heat to the tumor, homogenous heat distribution at every point of the entire tumor, and inherent problems with targeting indiscernible micrometastases, which cause reduced disease and death for patients.

Magnetic initiation HT is a method for killing cancer cells using magnetic fields. The temperature of the cancerous tissue can be elevated in the range of 42–46 °C, by indirect heating produced by several magnetic supplies connected to the tumor. Ferro-, ferri- and super ferromagnetic materials are appropriate for this treatment method. An important demand of any material is biocompatibility. One common material used in current studies is Fe/MgO. The heating capability relies on the material characteristics, such as magnetocrystalline anisotropy, and the size and microstructure of the nanoparticle. To allow them to enter the smallest portion of normal tissue or the cancer cell (which normally have diameters of 10 to 100 micrometers), MNP are prepared, that are nanometers in size. The particles used in HT display ferro- or ferrimagnetic characteristics.<sup>37</sup>

### *Combining hyperthermia and other treatment strategies*

HT is rarely used as a sole cancer treatment method and is typically added to different cancer treatments.<sup>6,7,38</sup> For various combinations of treatment, research and clinical trials have been conducted concentrating on the treatment of many kinds of cancers, mainly those with poor treatment results (e.g., melanoma, soft tissue sarcoma, malignancies of the brain, head and neck cancers, lung, breast, esophagus, cervix, colon, bladder, and liver).<sup>6,7</sup> Some methods have verified the effectiveness of HT in combined treatment, but others have not.<sup>6</sup>

Because adequate heating of the entire tumor volume is difficult, and the reported response duration is short, the use of HT alone is not suggested.<sup>39</sup> It has been recognized for over three decades that tumor cells are considerably more sensitive to moderate HT in “fever-range” temperatures (41–45 °C) than normal cells.<sup>10,38</sup>

In some clinical trials, an improvement in local control and survival rates of patients with locally advanced superficial and pelvic cancers have been shown by adding local or regional HT to radiotherapy.<sup>10</sup> Moderate HT has been reported to

perform as a dose adjusting material that raises the therapeutic ratio of conventional therapy, improving the efficiency of a given dose without supplementary toxicity.<sup>11</sup>

Currently, HT added to radiotherapy treatment for breast cancer, melanoma, glioblastoma, head and neck tumors, and cervical cancer increases complete response and survival rates.<sup>20,40,41</sup> Higher temperatures can cause scorching, burns, pain or necrosis. In the case of HT alone, there may be inflammation of the heated tissue and ischemia because of blood clots or hemorrhage.

In general, thermal side effects are transient.<sup>6,41</sup> Since phase III clinical trials have shown benefits of combined HT and radiotherapy regimens for numerous malignancies,<sup>41</sup> it is important to recognize the mechanism that leads to improved tumor cell death.<sup>42</sup>

Some studies have revealed that moderate HT (42–45 °C) improves the cytotoxicity of chemotherapeutic drugs and that HT and chemotherapy present synergistic anticancer effects. It is thought that mild HT (temperatures lower than 41 °C) causes antitumor effects via immune regulation, but these results do not combine with the antitumor effects of chemotherapy to kill cancer cells. However, clinical reports have shown that chemotherapy achieves promising results in patients with body temperatures near 39 °C.<sup>43</sup> The local or systemic temperature rises related to HT may enhance the sensitivity of cancer cells to chemotherapeutic drugs, boosting immunity and quickening apoptosis of tumor cells.<sup>44</sup>

Most studies have proposed that the efficient temperature range for making HT-related antitumor effects between 42 °C and 45 °C.<sup>45</sup> However, the medical use of systemic HT 39–41 °C as an adjuvant to radiotherapy and chemotherapy is possible and produces beneficial therapeutic anticancer effects.<sup>46</sup> Mild HT and chemotherapeutic agents have synergistic antitumor effects that increase the cytotoxicity of these drugs to cancer cells. Therefore, it is important to identify proper temperatures for treatments that add the use of HT and chemotherapy drugs.<sup>47</sup>

Studies of HT approaches have shown that therapy alone is not sufficient to kill cancer cells, but HT can improve the cell-killing effect of cytotoxic drugs and radiation (thermal chemosensitization and thermal radiosensitization).<sup>38</sup> Equally, better response and survival rates were detected in patients

treated with HT and radiotherapy compared to radiotherapy alone in numerous phase-III trials, with a higher survival rate and minimal damage to normal tissues in the patients treated with HT.<sup>41</sup>

HT and radiation act synergistically, which results in an increase in cell killing even at lower temperatures. This is called thermal radiosensitization. It appears most pronounced in S-phase cells that are usually resistant to radiation alone. To quantify the synergistic effect of heat and radiation, the thermal enhancement ratio (TER) is used. The TER defines the amount of thermal radiosensitization by the quotient of the survival fraction after radiation alone and in combination with HT.<sup>48</sup>

In experimental studies, HT inhibited the repair of radiation-induced DNA damage, thus increasing the cytotoxic effect of radiotherapy.<sup>49</sup> HT also improved blood flow, which may increase tissue oxygenation and make cells more sensitive to RT.<sup>50</sup> HT, which can cause cell death and stimulate the immune system, has been utilized for several decades as a cancer therapy.<sup>51</sup>

Apoptosis (cell death) is a strictly-controlled cell response and is essential to host defense and cancer control.<sup>52</sup> Apoptosis is thought to induce HT-caused cell death by causing intracellular oxidative stress.<sup>38</sup> Deficient apoptosis can encourage carcinogenesis and tumor development as many anticancer treatments work by causing apoptosis in cancer cells.<sup>53</sup>

Similarly, in palliative situations and recurrent cancer, HT was shown to preserve local progression free survival when joined with radiochemotherapy.<sup>54</sup> The synergic effect of heat and radiation relies on the time interval between the two treatments, the temperature used, and the treatment order. When the two methods are implemented concurrently, the response is greater, and this method is preferable. As shown in *in vitro* models, a supra-additive result of heat and radiation may arise when Chinese Hamster ovary (CHO) cells are heated before radiation for eight hours or more at temperatures more than 43 °C. When using radiation before the heat, a comparable effect is frequently detected when the heating period is shorter (two to four hours) and at temperatures less than 42 °C. A concurrent effect of the combination of radiation and heat can also be detected in thermotolerant cells when single radiation doses of 2–4 Gy is used, but this result may change depending on the cell type and tolerance.

Hypoxic cells, other than those with decreased nutrient supply and/or acidic pH, have been revealed to respond very sensitively to the combined heat and radiation.<sup>48,55,56</sup>

HT also improves the cytotoxicity of different antineoplastic drugs. The degree of a drug's thermal chemosensitization can also be given by the TER factor, which is the ratio of cell survival at the higher temperature to regular temperature for a definite drug dosage. Using HT, extra interactions between drugs and heat have been observed. For example, some drugs lose their chemical strength at advanced temperature, or are damaged by contact with glass or plastic.<sup>57</sup> Therefore, the addition of HT with chemotherapeutic drugs administration may decrease the effective of the dose and improve cancer cell response.<sup>33</sup>

The interaction between HT and chemotherapeutic agents has classified as 'additive', 'supra-additive' (having a linear increase with raising temperature), 'threshold-behavior' (obvious rise of cytotoxic effect above a distinct threshold temperature), and 'independent' (no reliance at all).<sup>58,59</sup> It is believed that most alkylating agents and platinum agents have supra-additive cytotoxic effect when temperatures are increased from 37 °C to above 40.5 °C. An additional set of drugs, thermosensitizers, has a cytotoxic effect when applied in high temperatures. Some familiar drugs like lidocaine or amphotericin B have been proven to perform as thermosensitizers.<sup>60</sup> Drugs that work better at standard temperatures do not essentially have a higher sensitization ability at elevated temperatures. Thermal chemosensitization may not be observed because the interval between drug administration and heat application is insufficient.<sup>57</sup>

While *in vitro* and *in vivo* trials identified that concurrent delivery resulted in larger thermal improvement ratios than sequential delivery. Concurrent treatments have not been examined with human patients due to logistical problems.<sup>51</sup>

## DISCUSSION

Local and regional HT approaches may offer greater therapeutic advantages than WBH. In several situations, the application of HT with different schedules of radiotherapy is advantageous.<sup>41</sup> Improvements are still necessary for local and regional HT procedures.

Many studies combining HT with new treatment modalities have concluded that to develop clinical outcomes of these procedures there is a need to improve the technologies available.<sup>6</sup>

Animal studies on 'mild' WBH (using temperatures between 40.5 °C and 42 °C, for 60–360 min) and some clinical trials propose an anticancer action of clinical HT even at these temperatures.<sup>41</sup> The clinical practice of using local and regional applicators needs development. Better temperature control may be obtained by using magnetic resonance tomography (MRT) combined with HT control methods.<sup>41</sup>

## SUMMARY

HT has cytotoxic effects on tumor cells. The sensitivity of tumor cells to heat are higher than normal cells, so they would be destroyed after HT treatment at 42 °C for two hours. Owing to their great thermosensitivity, the temperature of tumor cells is 3–7 °C greater than that of adjacent normal cells when heating. Hence, suitable HT will directly eradicate tumor cells without damaging nearby normal cells.<sup>61,62</sup>

Tumor cells that are insensitive to radiotherapy are those that are in the S-phase of the cell cycle or a hypoxic environment. However, these cells are highly sensitive to HT.<sup>61,62</sup> Furthermore, HT can prevent tumor cells being repaired after radiotherapy.<sup>61,62</sup> Due to the adequate blood supply in tumor adjacent tissues, the cytotoxicity of HT on nearby tissues is much less critical than that at the center of the tumor.<sup>63</sup>

Most of the time, an insufficient treatment response using HT results on marginal recurrence, but in radiotherapy treatment, tumor recurrence is due to the insufficient energy received by tumor cells. Therefore, using HT in combination with radiotherapy can have a synergistic effect on sensitizing cells.<sup>63</sup>

HT combined with chemotherapy can increase the cytotoxicity of some chemotherapy drugs, such as cisplatin. *In vitro* studies reported that the anti-cancer effect of chemotherapeutic agents can be enhanced 10 to 100 times after heating at 42 °C for two hours. Clinical trials have suggested that the efficiency of combined radiotherapy and chemotherapy treatments with HT were better than the value of each treatment alone.<sup>64</sup>

Although there is a reliable basis for using HT in some circumstances, we are unable to say in which situations HT should be implemented as a necessity. Many clinical studies will need to be reviewed together to decide which require which treatment.<sup>65</sup>

Based on the data currently available, we believe that the advantages of HT outweigh any negatives when used in combination with radiation or cytotoxic agents for special neoplastic diseases.

## CONCLUSION

HT can be applied by different methods, and this selection depends on the type of the tumor and its distribution in the body. Many studies confirm that HT could be an effective cancer treatment. However, particular methods need to be applied depending on the region. Moreover, HT in combination with basic cancer treatments like chemotherapy and radiotherapy can improve patients' survival rate.

### Disclosure

No conflicts of interest, financial or otherwise, were declared by the authors.

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