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# Hyperthermia: Role and Risk Factor for Cancer Treatment

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ABSTRACT

Over the past decades, cancer is the major cause of incidence of death increasing every day. Different forms of tumor therapy including radiotherapy and chemotherapy are used to treat cancer. However, hyperthermia is the technique that neglects the use of chemicals or harmful radiations. The elevated body temperature can damage the cancerous cells with minimum injury to the normal cells. Successful therapy method in combination with radiation therapy and/or chemotherapy is provided to the cancer patient which proved to be beneficial to the patients. In this review, different studies of the clinical trials are reported on the patients with tumor and the therapy associated with it.

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## Introduction

Hyperthermia (also known as thermotherapy) is generally regarded as a mean body temperature higher than normal (Alexander, 2008). High body temperature is often caused by illness, such as fever or heat stroke. Research has shown that elevated body temperature can damage and kill cancerous cells with minimal injury to normal cells (van der Zee et al., 2000).

*Abbreviations:* CEM, cumulative equivalent minutes; US, ultrasound; EM, Electromagnetic; DFS, disease-free survival.

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The main mechanism involved is by killing the cancer cells by destructing proteins and the structure within cells. Thus, hyperthermia may shrink tumors (Wust et al., 2002). Hyperthermia may make some of the tumor cells more prone to radiations or damage other cancer cells which cannot be damaged by radiation. Many times, it also increases the effects of certain anticancer agents. In this study, we would focus on use of heat to treat cancer. Hyperthermia is widely applicable with different other forms of cancer therapy, including radiation therapy and chemotherapy (Alexander, 2001). The aim of the study was to treat many types of cancer including brain, liver, sarcoma, lung, esophagus, breast, bladder, rectum and peritoneal lining (Kapp et al., 1990; van der Zee et al., 2000). There are over 100 types of cancers present in the world and are classified according to cell type. According to GLOBOCAN statistics analysis (2012), 14.1 million new cancer cases, 8.2 million cancer deaths and 32.6 million people living with death were reported (Ferlay et al., 2013). The American Cancer society in 2014 provided the annual report, according to which there will be an estimated 1,665,540 new cancer cases diagnosed (ACS). Hyperthermia is under clinical trials (research study with people) and is not widely available. However, while receiving those combination therapies, only few have shown increased survival in patients (Falk and Issels, 2001). Various techniques of hyperthermia are presently under investigation, that include local, regional and whole body hyperthermia (Feldman et al., 2003; Chang et al., 2001). Many of these have shown a significant depression in tumor size when hyperthermia is combined with other treatment or therapy. Attaining temperature above the systemic temperature 37 °C in a specified target volume is a challenge and still under development. High temperature is induced by applying a power density specific absorption rate (SAR; measured in W/kg). Normal basal metabolism of human is above 1 W/kg. Perfusion counteracts the elevated temperature. In humans perfusion rate is around 5–15 ml per 100 g per min, but they differ widely. To reach the elevated temperature approx 42 °C at least in some parts of the body tumors require a power density of approx 20–40 W/kg at the target region (Tilly et al., 2001). (See Tables 1 and 2.)

**Table 1**
Clinical trials on hyperthermia.

| Cancer site | Control therapy | Experimental work done | Primary endpoint | Survival benefit | Reference |
|---|---|---|---|---|---|
| Head and neck (primary) | Radiotherapy | Radiotherapy and local hyperthermia | Response at 8 weeks | No | Datta et al. (1990) |
| Melanoma | Radiotherapy | Radiotherapy and local hyperthermia | Complete response (Complete response) | No | Overgaard et al. (1995) |
| Superficial (head, neck, breast, miscellaneous) | Radiotherapy | Radiotherapy and local hyperthermia | Initial response | No | Perez et al. (1991) |
| Head and neck | Radiotherapy | Radiotherapy and local hyperthermia | Best response | Yes | Valdagni and Amichetti (1993) |
| Breast(advanced primary or recurrent) | Radiotherapy | Radiotherapy and local hyperthermia | Initial response | No | Vernon et al. (1996) |
| Breast cancer (Phase III) | Radiotherapy | Radiotherapy and hyperthermia | Disease-free survival | Yes | Jones et al. (2005) |
| Superficial (head, neck, breast, sarcoma) | Radiotherapy and 1× local hyperthermia | Radiotherapy and local hyperthermia | Best response | No | Emami et al. (1992) |
| Superficial (head, neck, breast, sarcoma) | Radiotherapy and 1× local hyperthermia | Radiotherapy and local hyperthermia | Initial response | No | Engin et al. (1995) |
| Superficial (head, neck, breast, sarcoma, others) | Radiotherapy 2× local hyperthermia | Radiotherapy and local hyperthermia | Initial response | No | Kapp et al. (1990) |
| Glioblastoma | Radiotherapy interstitial radiotherapy | Radiotherapy, interstitial radiotherapy, and interstitial hyperthermia | 2-year survival | Yes | Sneed et al. (1998) |
| Rectum (T4 locally advanced) | Radiotherapy | Radiotherapy and endocavitary hyperthermia | Initial response | Yes | Berdov and Menteshashvili (1990) |
| Esophagus (stages I–IV, neoadjuvant) | Radiotherapy and chemotherapy | Radiotherapy, chemotherapy, and endocavitary hyperthermia | Histological complete response | Yes | Kitamura et al. (1995) |
| Esophagus (stages I–IV, neoadjuvant) | Chemotherapy | Chemotherapy and endocavitary hyperthermia | Initial response | Yes | Sugimachi et al. (1994) |
| Stomach (T3, locally advanced) | Surgery | Surgery and hyperthermic intraperitoneal perfusion | 5-year survival | Yes | Hamazoe et al. (1994) |
| Melanoma (stages I–III) | Surgery | Surgery and hyperthermic isolated limb perfusion | Disease-free survival | Yes | Ghussen et al. (1984) |
| Melanoma (stages I–III) | Surgery | Surgery and hyperthermic isolated limb perfusion | Disease-free survival | No | Koops et al. (1998) |
| Primary or recurrent pelvic (cervix, rectum, bladder) | Radiotherapy | Radiotherapy and regional hyperthermia | Complete response | Yes | Van der Zee et al. (2000) |
| Localized tumor (phase III) | Radiotherapy with superficial hyperthermia | Radiotherapy with superficial hyperthermia | Partial response | Yes | Vernon et al. (1996) |

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*Local Hyperthermia*

Local hyperthermia is a technique in which heat is applied to a small area, such as tumor in a tissue, using different techniques that deliver heat energy to the tumor. Different techniques were used to incorporate heat like as microwave, ultrasound and radiofrequency. On the basis of tumor location, there are several approaches for local hyperthermia.

| S. no. | Approach | Application |
|---|---|---|
| 1 | External | Used to treat tumors that are in or just below the skin. External applicators are focused on or around the affected area to raise its temperature. |
| 2 | Intraluminal or endocavitary | Used to treat the tumors within the body or near body cavities, like as esophagus or rectum. Probes were placed inside the cavity and then inserted into the tumor to deliver energy and heat the area directly. |
| 3 | Interstitial | Used to treat the tumors which were deep inside the body, such as brain tumors in which high heat is required then the external technique, such as ultrasound — may be used to make sure that the probe is properly positioned within the tumor. Radiofrequency ablation is a technique that requires the waves to heat and kill the cancer cells. |

By means of antennas or applicator emitting microwaves or radiowaves, superficial tumors can be heated, when placed on their surface with a contacting medium. Various applicators have been clinically used such as horn spiral, waveguide applicators, compact applicators and current sheet. Intratumoral temperature can be controlled by providing the position to the applicator. For the local hyperthermia, QA guidelines have been developed. Multiapplicator or dual applicator operation would be better, but these were not commercially available.

*Interstitial and Endocavitary Hyperthermia*

In this method, applicators were inserted within the tumor and in several cases heat therapy was administered along with brachy therapy. The treatment is administered along with brachytherapy by the afterloading method in a close connection of area to be heated. That technique was useful for the tumors that were less that 5 cm in diameter. Several antenna types were available, including microwave antennas, radiofrequency electrodes, ultrasound transducers, heat sources (hot water tubes, ferromagnetic seeds), and also fibers. Target volume needs a distance between adjacent applicators of not more than 1.0–1.5 cm but that positioning is very painful. Because of their sensitivity to interference, orientation and positioning of microwave antennas could be critical. These systems are undergoing clinical evaluation. Endocavitary antennas were inserted in openings of hollow organs such as the urethra (prostate), rectum (rectal cancer, prostate), esophagus, cervix and vagina. On the surface of the body, counter electrodes were applied to generate power deposition surface.

**Table 2**
Studies on different types of tumor using hyperthermia technique.

| S. no | Author | Work done | Year |
|---|---|---|---|
| 1 | van der Zee J.et al. | Organized a multi centric trial on 358 patients & observed that in bladder tumor CR rate increased from 51% to 73% and in cervix cancer from 57% to 83% when hyperthermia along with radiotherapy is given. So, the survival rate is increased from 27% to 51% as compared to hyperthermia alone. | 1993 |
| 2 | Valdagni R. et al. | An Italian phase III study on head and neck cancer (stage IV) revealed that combination therapy of hyperthermia and radiotherapy increased the CR rate from 41% to 83%, with a 5-year local control rate from 24% to 68%. The 5-year overall survival rate is increased from 0% to 53% as compared to radiotherapy alone. | 1994 |
| 3 | Overgaard J. et al. | A Danish phase III study on 70 patients suffering from *relapse or metastatic melanoma* concluded that the CR rate is 62% with hyperthermia-radiotherapy combination and 35% with radiotherapy alone. Five year DFS is 28% with radiotherapy and 46% with combination therapy. | 1996 |
| 5 | Wang J. et al. | A Chinese study published on 125 patients with *esophageal cancer*, either treated by radiotherapy in combination with chemotherapy with or without regional hyperthermia. The study concluded that almost two fold increase in 3-year OS (with hyperthermia — 42%, without hyperthermia — 24%) | 1996 |
| 7 | Issels RD | In a German phase III study consisting of 342 patients affected by high risk *sarcoma*, when treated with neo adjuvant chemotherapy and radiotherapy with or without hyperthermia. Patients when treated with hyperthermia reported 50% reduction in tumor volume as compared to 12% in the group without hyperthermia. | 2007 |
| 8 | Heijkoop | Studied about triple therapy combination containing regional hyperthermia, chemotherapy and branchy therapy for the treatment of advanced *cervix cancer*. | 2012 |
| 9 | Schroeder | Evaluated the effect of regional hyperthermia along with neo adjuvant chemo-radiation on rates of complete pathological response. Neo adjuvant chemoradiation with or without regional hyperthermia is provided to the patient in a no-randomized fashion. | 2012 |
| 10 | Barsukov | For advanced rectal cancer, a phase II study was performed n 64 individuals by combining hyperthermia along with chemo-radiation. Chemotherapy and hyperthermia in combination are utilized when performed in 59 subjects (92.2%). Overall survival (2 year) was 91% and disease free survival (2 year) was 83%. Study limitations include lack of randomization and lack of a control group. | 2013 |

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*Side Effects of Local Hyperthermia*

Side effects of local hyperthermia is that it might lead to pain at the target site, bleeding, blood clots, infection, swelling, burns, blistering, and also cause damage to skin, nerves and muscles around the treated area.

In *regional hyperthermia* a body part such as limb, organ, or body cavity (a hollow space within the body) is heated. These can be heated by arrays of antennas by using different applicators. Sigma blade applicator is a widely used applicator that contains four pairs of dipole antennas in a ring around the patient. Model calculation showed significant enhanced control of power distribution by increasing the antenna number. It also includes the assumption of optimum adjustment of phrases and amplitudes (Seebass et al., 2001). The additional variable would be RF frequency (100–150 MHz).

*Whole Body Hyperthermia*

Whole body hyperthermia is applied to treat metastatic tumor that has spread throughout the body. A steady state of 42 °C is maintained for 1 h along with the acceptable adverse effects. With the help of sedation of general anesthesia, the procedure would be possible. Application of intubation for the safe administration is still under research. In interaction with the various anesthetics, as compared with local regional methods, an entirely different range of toxic effects arises from the systemic stress (Bull et al., 1982; Kerner et al., 1999). A patient weighing about 70 kg at 37 °C has a basal metabolic rate of 85 W and double that at 42 °C; that in itself was enough to raise the body heat within 180 min between 37·5 °C and 42·0 °C. The power distribution is influenced by three-dimensional anatomy. The transforming network might lead to further limitations in antenna control, as the antenna properties at the feed points were disturbed by coupling and imperfect geometry (Wust et al., 2002). One of the next generations of commercially available applicator was sigma-Eye applicator consisting of three shorter rings, each with four flat dipole-antenna pairs. Magnetic resonance tomography provides treatment monitoring which could characterize temperature as well as perfusion.

*Side Effects of Regional and Whole-body Hyperthermia*

Side effects of regional and whole-body hyperthermia are that it could lead to nausea, vomiting, and diarrhea. In severe cases (rarely) it leads to problems associated with heart, blood vessels, and other major organs. The adverse effects of regional and whole body hyperthermia along with that of other cancer treatments might be possible. But improved technology, experience, and better skills led to fewer side effects. Generally the problems associated with hyperthermia are not serious.

## Hyperthermia in Association With Radiotherapy

Hyperthermia enhances the oxygenation and perfusion of hypnotic cells, where the ionizing radiation increases three times more than the normal cells. As a result, radiotherapy activity becomes 1.5–5 times more proficient. Hyperthermia has a direct effect on the tumor cells. It acts mostly in the S phase of the cell cycle at an acidic pH, when the cells are radio-resistant. Hence, radiotherapy and hyperthermia are complementary in their action: free radicals are formed from radiotherapy, which thereby damage the DNA of the tumor cells and hyperthermia inhibits its reparation. Radiation damage inhibited by hyperthermia has been an important factor which leads to the synergistic killing effect of the X-rays and hyperthermia. Before the X-irradiation, heating cells have shown to inhibit the DNA strand breaks as well as the excision of base damage (Kampinga and Konings, 1987). Various DNA repair pathways are involved in re-establishment of damage after ionizing irradiation. Heat shock affects the kinetics of all of them. Data reported in 2004 revealed that the thermal inhibition of the non-homologous end-joining pathway plays a role in thermal radio sensitization. However, few data suggested that the homologous recombination pathway may not be the major heat target. Deduction could be the crucial step in the mechanism of radio-sensitization by heat for the inhibition of base-excision (Kampinga et al., 2004). Hyperthermia increases the sensitivity of cells towards radiation and drugs and this sensitization is not directly related to altered heat-shock protein (HSP) expression. Elevating HSP prior to heating makes cells thermo-tolerant and changing their expression will automatically affect the extent of thermal action because the HSP will attenuate the heat-induced protein damage, which is responsible for drug sensitization and radiation. Base-excision damage repair and other hypothermic effects on DNA repair occurred due to nuclear protein damage (Kampinga, 2006).

## Hyperthermia in Association With Chemotherapy

Hyperthermia drug sensitization can be found in several anti-cancer drugs, mainly in alkylating agents. Those cells which are already resistant to the drugs, can respond to the same drug with combination therapy (i.e. heat). Hyperthermia, with enhanced tissue perfusion, facilitates the absorption of chemotherapeutic API through cell membrane. In the presence of heat, chemical reaction gets accelerated. Therefore, chemotherapy becomes more effective, and less toxic. A targeted chemotherapy with reduced side effects are provided when, liposomes including adriamycin (Caelyx®) are administered through i.v. Hyperthermia fuses and free its content inside the heated tumor bed. A clinical study of hyperthermia along with radiotherapy was associated from 1989 to 1998. Clinical data allowed obtaining the proof sufficient to establish some recommendations for significant use of hyperthermia (Shrivastava et al., 1989). In Osaka in the year 2004, a clinical group was founded (Kadota Fund International Forum, Kadota, Japan), and its conclusion was published in year 2008 for chemotherapy long with hyperthermia (Emami et al., 1991). The first

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review was published in 1989 and evaluated the results of non-randomized studies of 24 authors from the USA and Europe on 2234 patients were affected with various types of cancer including — breast cancer, head and neck tumor (Valdagni and Amichetti, 1994). The paper demonstrated that the 36% cancer rate obtained with exclusive radiotherapy was almost doubled with hyperthermia in combination with radiotherapy. Multicentric investigation showed that combination therapy of hyperthermia with radiotherapy improves the results when compared with the radiotherapy or hyperthermia alone.

*Treatment Planning and Simulation*

Planning for individual therapy is important, due to tumor geometry, shape, size and varying tumor location. The first hyperthermia treatment step includes — creation of a human model by segmentation of images, from MRI or computerized tomography. Online parameter identification on the basis of MRI is performed in certain cases. Using this segmentation and a model of applicator, the power absorption or specific absorption rate distribution is calculated in the patient by electromagnetic models. The EM model for treatment planning is generally based on finite-difference time-domain (FDTD) or finite element method (FEM). The heat distribution in the patient is calculated from the power absorption distribution by using Pennes' bio-heat equation (PBHE), more elaborate algorithms consisting the blood vessel networks i.e. discreate vasculature models (DIVA), down to vessel sizes (millimeter). The problem associated with these thermal method generation of vessel network requires-long time, poorly — predictable, variation in thermal properties of tissues. The main aim in the treatment planning is to heat a specific tumor. Also delivering at least 43 °C to 90% of its volume for cumulative in multiple treatments for more than 10 min corresponds to doubling of the possibility for complete response and duration of response to combination of hyperthermia and radiotherapy versus radiotherapy alone (Oleson et al., 1993).

As for now CEM at 43 °C obtained 90% of tumor volume which appears to be the highly useful dosimetric parameter in clinical research. Treatment planning on the basis of tumor cell survival has been planned for thermo seed placement. But till now either ad hoc cost functional based on the thermal distribution or on the absorption rate density has been used for regional hyperthermia (van der Zee et al., 2007). In therapy planning of local-regional hyperthermia using RF as the heat source, the therapeutically optical antenna as the parameter for the applicator is determined for each patient. By solving Maxwell equations, the specific absorption rate values are obtained. Also, by using bio-heat transfer equation, the temperature distribution is predicted. This planning greatly improves the quality of medical treatment with a virtual experiment to model, and optimizes the therapy with high accuracy (Crezee et al., 2005).

Motivations for simulation:

1. With treatment preplanning, it provides better heating.
2. Optimize setups for treatment cases.
3. Assist new applicator proposal in the future.

Due to auto-regulation capabilities of the tissue, the perfusion depends on the temperature. Moreover, the systemic thermo-response plays an important role at least in abdominal hyperthermia. Various perfusion models have been designed, which covers a broad spectrum of homogenized and discrete vascular models. A mathematical model of the clinical system (8 antennas within radio frequency applicator, individual patient body, water bolus) which contains Maxwell's equation in homogenous media therefore, called as bio-heat transfer PDE describing the temperature distribution in the human body. The electromagnetic field and the thermal phenomena need to be computed at a speed suitable for the clinical environment (Weiser, 2008).

**Instrumentation: Applicator, Temperature Determination, Bolus, and Monitoring**

Hyperthermia can be applied by interstitial/intra-cavitary, external or whole body techniques (applicators). External hyperthermia applicators utilize US or EM waves to direct the energy to the target region. US and EM both provide similar heating problems but US results in higher bone-pain complaints during therapy (Yosef and Kapp, 1995). Generally, in hyperthermia two types of probes are required. The first one is required to deliver the energy to the tissue, another for tissue temperature monitoring. During treatment, tumor temperature is measured by temperature sensors. Temperature optimization is done by using automatic computer controlled regulation of the applicator power output. Thermometer probes available commercially are:

- Thermocouple
- Non-perturbing probes
- Thermistors
- Thermistor sensor with high-resistance plastic leads containing graphite
- Optical fibers
- Fluorescent-type sensor made of two phosphorus
- Semiconductor crystal
- Liquid crystal sensor
- Birefringent sensor of $LiNbO_3$
- Multiple thermistor sensors with high-resistance leads.

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Non-invasive thermometry

- Microwave multi-frequency radiometry
- Computerized tomography (CT) for thermometry.
- Nuclear magnetic resonance
- Electrical impedance tomography.

The thermometers based on optical fibers do not disturb the electromagnetic fields, as they offer an advantage of not possessing metallic components. The energy is delivered to the patient's body through a probe, which is usually referred to as the applicator. The applicator including the bolus is placed on the patient's skin. So, it remains in touch with the skin. This bolus is then filled with circulating water that can be heated as necessary for the treatment.

The bolus can be used to induce electromagnetic waves into the patient body as it has advantages of reducing reflection and waste of energy. Heating is performed with external antennae or intracavitory probes by an induction phenomenon. In order to ensure local heating at a specific site, ferromagnetic material can be used. For surface tumors, microwave heating at 434 MHz to 915 MHz is used while RF at 8–12 MHz is useful for heating of the deep-seated tumor. Heating with ultrasound is also feasible.

## Conclusion

Hyperthermia is today an important treatment modality in the treatment of cancer, and its results are strongly supported by the criteria of evidence based medicine. Hyperthermia in addition to radiotherapy with or without chemotherapy is important when it is necessary to treat advanced or high-risk tumors, or to retreat a relapse in a pre-irradiated area. Hyperthermia appears to be the fourth pillar besides surgery, radiotherapy and chemotherapy. Its diffusion is to be hoped for because, against the common enemy, four weapons are better than three.

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