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**Review Article**

# Hyperthermia: A Neoadjuvant Therapeutic Approach in Cancer Treatment

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## ABSTRACT

Hyperthermia refers to elevation tumor temperature from 39 up to 43 degree Celsius. Actually Therapeutic Hyperthermia has been used as an adjuvant treatment for cancer, since end of the 19th century after observations William Coley who found that tumor is diminished after induction of fever by bacterial toxins. Hyperthermia therapy refers to treatment tumors through heating which has been used since the time of the ancient Egyptians. The term 'Hyperthermia' in oncology means treatment of malignant disease by heating in different ways. Hyperthermia is usually applied as an adjuvant therapy method in combination with other modalities such as Radiotherapy or Chemotherapy in cancer treatment. Typically there are three categories for Hyperthermia, including local, regional and whole body. Based on the temperature Whole body hyperthermia classify in 3 type, mild, fever range and extreme. In Mild hyperthermia, the temperature is from 37.5 up to 38.5 degree Celsius, in fever range hyperthermia, 38.5 up to 40 degree Celsius, and extreme hyperthermia, the temperature above 40 degree Celsius. Now Days Whole body hyperthermia known as immunotherapy related to cancer treatment in oncology. Here we will review whole body hyperthermia related to cancer treatment.

**Keywords**: : Cancer, Immune Effectors, Hyperthermia

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Typically there are three categories for Hyperthermia, including local, regional and whole body (1). Local Hyperthermia is used to solid ,localized and superficial tumors while regional is generally used for deeper diseases, and whole body Hyperthermia typically used for metastatic cancers (2). Whole body hyperthermia devices uses water-filtered infrared radiation (wIRA) emitters by four wIRA emitters to the upper zone, and two WIRc emitters for warming the lower limb of patients (3). The most common method in whole body hyperthermia is used of infrared chamber (4).

Other methods may administrate through patient ,s room or warping the patient in heated blanket (1). Actually the exact mechanism of direct HT-induced cell death is not well understood (5).

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**Mechanisms of Action of Hyperthermia**

Actually the exact mechanism of direct HT-induced cell death is not well understood (5). Certainly clinical effects of Hyperthermia is more Based on it 's combination with other modalities, and it is more important, it can sensitize tumor cells to other forms of therapy, including RT (Radiation Therapy) and chemotherapy (CT). Molecular effectors of hyperthermia include; Cell membrane alterations in fluidity, stability, changes in structure; stability of plasma membrane, membrane potential, cell surface receptors, transmembrane transport mechanisms, apoptosis, impairment of ion transport ($Ca^{2+}$, $Na^{+}$, $Mg^{+}$, $K^{+}$); impairment of protein synthesis, Induction of HSP synthesis, generation of reactive oxygen species (ROS), impairment of RNA/DNA synthesis, inhibition of DNA-repair mechanisms, modification of gene expression, signal transduction Inhibition of DNA repair enzymes, and protein synthesis (impaired), miss folding, denaturation /nuclear aggregation (6-9). Although the role of HSPs is still under investigation, current evidence has proved that enhanced immunogenicity and HSP expression seen after tumor cells are heated, thermally enhanced immune effector cell activation and function, thermally enhanced vascular perfusion and delivery or trafficking of immune effector cells to tumors (10, 11). Due to their unique immunologic features, HSPs are induced by hyperthermia known as specific immunogenic effectors (12, 13). To regard as many Studies that have demonstrated immunological effects of fever range whole-body hyperthermia (FR-WBH), The most important role of elevation temperature in fever range is immunological effects. It is now appreciated that heating tumors (in situ) can activate vascular, metabolic, and immunologic parameters of the tumor microenvironment which may play an additional role in radiochemosensitization beyond hyperthermia induced cell killing of tumor cells (14, 15). The extent of the interaction of heat and radiation can be expressed in terms of the thermal enhancement ratio (TER), defined as the ratio of doses of x-rays required to produce a given level of biologic damage with and without the application of heat. TER have been estimated to be in range of 1.5 for several human tumor type. Jones and colleagues reported that mild hyperthermia (41° and 41.5° C at 90% of the measured points for 1 hour) significantly increased the $po_2$ in hypoxic.

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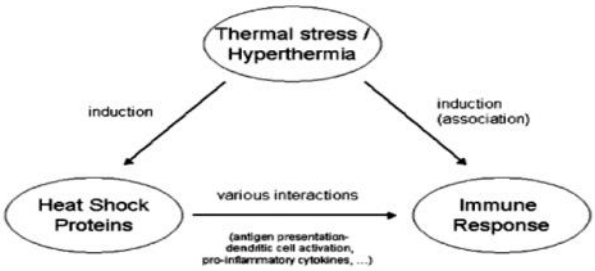


Figure1:The interaction between Hyperthermia and immune system based on Repasky 's study.

Such increases in tumor oxygenation could significantly improve tumor response to radiotherapy and is likely to be the primary important effect of local/regional or whole body forms of clinical hyperthermia. 'Thermalradiosensitization' results in a reduction of the shoulder of the dose–effect curve. It appears most pronounced in S-phase cells that are usually resistant to radiation alone . Also HT can increase perfusion to tumors, making them more susceptible to RT and increasing cell-killing (16).

**Clinical Use of Hyperthermia**

A randomized clinical trial carried out by Jones et al-2005,Has reported CR rates of 23.5% for radiotherapy alone versus 68.2% for hyperthermia plus radiotherapy (4). To regard as many studies that have demonstrated immunological effects of fever range whole-body hyperthermia (FR-WBH) , the most important role of elevation temperature in fever range is immunological effects (5). Although the role of HSPs is still under investigation, much more work is needed, current evidence has proved that enhanced immunogenicity and HSP expression seen after tumor cells are heated, thermally enhanced immune effector cell activation and function, thermally enhanced vascular perfusion and delivery or trafficking of immune effector cells to tumors(10, 11). Based on Table 1, Several phase III trials exploring HT with RT have been performed since the 1980s and are published but neither phase III studies of local nor whole body have been done on the whole body hyperthermia for metastatic cancers .Just phase I study by Bell et al. explored the application of whole body Hyperthermia plus CT using an infrared radiant heating device as part of a regimen which included cisplatin, gemcitabine, and INF-a for chemotherapy-resistant metastatic or other advanced solid malignancies (4). In Phase I/II studies at University of Texas, Medical School at Houston, fever range hyperthermia plus chemotherapy ,at April 2008 that career out JM Bull et al ,the good response were observed in patients with high grade neoroendocrine and pancreas cancer. The complete and partial responses combined were 43 % (17). A more recent trial from Duke University Medical Center randomized patients between RT and HT + RT for superficial tumors≤3 cm in depth. Tumors were mostly in the breast and chest wall region (64%), but also included

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**Table 1. Ligands with corresponding cancerous cell surface specific antigens**

| First author (Year) | Site | # Pts | Arms | Local Control | Overall survival |
|---|---|---|---|---|---|
| Van der Zee (2002) | Cervix | 56 | 48.3 Gy EBRT + 18 Gy brachy boost | 37% (12 yr) | 20% (12 yr) |
| | | 58 | Additional HT 1x/week | 56% (12 yr) | 37%(12 yr) |
| Harima (2001) | Cervix | 20 | 52.2 Gy ERBT + 30 Gy brachy boost | 48.5% (3 yr) | 48.1%(3 yr) |
| | | 20 | Additional HT 1×/week | 79.7%(3 yr) | 58.2%(3 yr) |
| Vasanthan (2005) | Cervix | 55 | EBRT + brachy (variable) | 68.5%(3 yr) | 73.2 (3 yr) |
| | | 55 | EBRT + brachy + HT 1×/week | No sig. diff. | No sig. diff. |
| Vernon (1996) | Breast | 135 | EBRT (variable) | 69.1%(2 yr) | 41%(2 yr) |
| | | 171 | EBRT + HT | 83.2%(2 yr) | 36%(2 yr) |
| (2011) | Bladder | 41 | MMC | Outcomes were 10-year KM estimated DFS (52.8%vs. 14.6%in the control group) | |
| | | 42 | MMC + HT | | |
| Van der Zee (2002) | Bladder | 49 | EBRT | 33% | 22% |
| | | 52 | EBRT + HT | 42% | 28% |
| Jones (2005) | Superficial sites | 52 | No HT (mean 41 Gy) | 25% | ~12%(7 yr) |
| | | 56 | HT | 48% | No sig. diff. |
| Valdagni (1994) | Head & neck metastatic to lymph nodes | 22 | EBRT | Not reported | 0%(5 yr) |
| | | 18 | EBRT + HT | Not reported | 53.5%(5 yr) |
| Huilgol (2010) | Head & neck (non-metastatic) | 26 | EBRT | Outcomes were pCR (78.6%vs. 42.4%in the control group) and median survival (241 days vs. 145 days in the control group) | |
| | | 28 | EBRT + HT | | |
| Sneed (1998) | Intracranial (glioblastoma multiforme) | 39 | 59.4 Gy EBRT + later 60 Gy brachy boost | Not reported | 15%(2 yr) |
| | | 40 | Additional HT (43 °C) with brachy sessions | Not reported | 31%(2 yr) |
| Mitsumori (2006) | Lung (non-small cell) | 40 | EBRT | Not reported | 38.1%(1 yr) |
| | | 40 | EBRT + HT | Not reported | 43.0%(1 yr) |
| Overgaard (1995) | Skin (melanoma) | 65 | EBRT (24 Gy or 27 Gy) | 28%(2 yr) | 19% overall 5-year survival; greater (38%) for patients with controlled disease compared to persistent disease (10%) |
| | | 63 | Additional HT (43 °C for 60 min) | 46%(2 yr) | |
| Schroeder (2012) | Rectum | 45 | 50.4 Gy EBRT + chemotherapy | This study measured pCR as an outcome: 6.7%in no-HT group vs. 16.4% in HT group. | |
| | | 61 | Additional HT (minimum 40.5 °C for 60 min) | | |
| Issels (2010) | Soft tissue sarcoma | 172 | EIA | 55%(4 yr) | 59%(4 yr) |
| | | 169 | EIA + regional HT | 66%(4 yr) | 57%(4 yr) |

head and neck (13%), melanomas (10%), and other regions (12%) (4, 18, 19). A randomized clinical trial carried out by Jones et al-2005 Has reported that CR rates of 23.5% for RT alone versus68.2% for HT + RT. At now a large number of studies document effectiveness of clinical effectiveness of hyperthermia plus RT or CT in vivo whether or in vitro condition, and also several clinical trial studies comparing have shown beneficial effects of hyperthermia with RT and or CT. In spite of many studies about HT , mechanism of it is unclear (5). Also HT can increase perfusion to tumors, making them more susceptible to RT and increasing cell-killing (16). Such increases perfusion to tumors could significantly improve tumor response to radiotherapy and is likely to be the primary important effect of local/regional or whole body forms of clinical hyperthermia (4).

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**Conclusion**

hyperthermia can be used in combination with other modalities such as radiation therapy or chemotherapy that can have additive effect on the modalities. Actually a large number of studies document clinical effectiveness of hyperthermia in combination with RT or CT in vivo and/or in vitro condition. In spite of many studies which has been published about HT, at now the exact mechanism of it is unclear. Here we review type of method and description of cellular basic of hyperthermia related to cancer treatment and summaries the clinical data have been documented effects of hyperthermia in combination with other modalities. Despite of many study up to now, the actual mechanism of hyperthermia related to cancer immunology effects is unclear, so much more work is needed to understood this interaction.