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RENIASSANCE OF HYPERTHERMIA AN ADDITION OF A NEW THERAPEUTIC OPTION

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I. INTRODUCTION

Heat as a therapeutic modality to treat various illnesses has been recorded in various ancient compendiums written by Shushruta, Charaka, Galen and Hippocrates. Heat as a treatment option has continued in the traditional system of Ayurveda. Hyperthermia for the treatment of cancer was shown to be effective in 1866. Later in 1893 William Coley demonstrated disappearance of malignant lesions in patients with high fever. However, his attempt to treat patients with cancer by inducing fever did not become popular due to unpredictable toxicity. Later in 70's hyperthermia had a new birth with newer technologies.

An international effort was initiated in the first international congress on hyperthermic oncology held in Washington in 1975. This international effort was preceded by the individual efforts in USA, Europe, and Japan. Hyperthermia as a modality of treating cancer gained a quick acceptance in the 70's. The limitations of the technology were overlooked amidst the enthusiasm of the newfound technology. Soon the interest waned as not many randomized trials could show the benefits of hyperthermia. Technology has improved ever since then. There are more positive randomized trends now. This review will address rationale for hyperthermia, technology and clinical results. There is an overwhelming evidence to pursue HT as an adjuvant to radiation.

II.BIOLOGICAL BASIS FOR HYPERTHERMIA

Cells when heated to a temperature of 45°C tend to lyse either by apoptosis or mitotic death. Heat in the range of 42°C to 45°C, can also sensitize cells exposed to ionizing radiation or chemotherapy. One of the important mechanisms of action leading to cell death is probably protein denaturation, observed at temperature of >40°C, which leads to, among other things, alterations in structures like cytoskeleton, membranes, and changes in enzyme complexes for DNA synthesis and repair[2].

Heat also is known to affect cell membrane, a target not shared with ionizing radiation. Hypoxic cells, which are generally resistant to ionizing radiation, are sensitive to heat. Acidic environment of tumour confers resistance to radiation but favours cell kill due to heat. This also gives a window for therapeutic intervention with heat, as normal tissues, are well perfused and have no acidic environment.

Heating cells at 42°C for 10 minutes leads inhibition of DNA synthesis by 40 percent while, it is 90 percent at 45°C for 15 minutes. Heat can induce cell death in non-dividing cells by activation of various enzymes[3].

Thus hyperthermia in the range of 42°-45°C is sown to be cytocidal and a good sensitizer of ionizing radiation. It is also shown to have synergistic effects with Bleomycin, Adriamycin and Platinol derivatives. The synergistic effects of, chemotherapy with hyperthermia is due to spatial co-operation. Increased perfusion due to health improves drug delivery to the tumour. It also ensures increased intracellular uptake of the drug as well as repair inhibition of DNA damage due to cytotoxic drugs. Combination of hyperthermia and chemotherapy also has shown decreased drug resistance.[4] Interestingly an enhancement ratio of 23 was shown in cell lines when cell lines in were treated with Melphalan and heat at 44°C[5].

III. HEATING TECHNIQUES

There are various techniques of heating loco-regionally or systemically. Immersion in temperature controlled hot water bath and radiant heat with U.V. are the usual techniques for whole body hyperthermia. Extracorporeal heating for the treatment of AIDS has also been reported. However, efficient loco-regional heating of tumour site can be done with electro-magnetic waves generated in RF and microwave range. Heating could be capacitative or inductive. Heating could be with external antennae or with interstitial and intracavitory probes. Intracellular heating with

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ferromagnetic material with a desired Curie point subjected to alternating magnetic field can also generate localized heating. RF at 8-12 MHz is useful for heating of the deep-seated tumour while, microwave heating at 434 MHz to 915 MHz is useful in surface tumours. Pain and thermal burns are the limiting toxicities of the techniques. Heating with ultrasound is also feasible.

Mechanical ultrasonic waves delivered at 0.2-5MHz. Can effectively heat a small volume at various depths efficiently. Pain and unpredictable heat deposition at tissue bone or tissue air cavity can be a limiting technological factor. Scanning transducers can overcome this difficulty. Ultrasound heating, unlike imaging has not gained popular use in the clinic.

IV. TOXICITY

Toxicity related to hyperthermia include pain and thermal burns. There is no evidence that addition of hyperthermia increases the toxicities of either radiation or chemotherapy. However, post surgical site may be more susceptible to heat due to poorly vascularised state. Skin and subcutaneous tissues are generally susceptible to increased power deposition when heated with microwave and radiofrequency waves. Thermal burns which are superficial and generally heal quickly are seen in 2-15% of the patients[6].

V. CLINICAL EXPERIENCE

Initial studies showed a consistently better outcome following hyperthermia alone. A review of 14 studies which, included 343 patients reported a complete response of none to 40% (over all 13%) and a partial response of 0 to 56% with an objective overall response of 51%[8]. Many studies have consistently shown a marked improvement in response rate (Table 1). A total of 713 patients were collated and the response analyzed. Addition of hyperthermia to radiation showed an improvement in complete response from 31% to 65%[9].

The role of chemoradiation with hyperthermia is being explored in cervical cancer by Zee et. al. (Personal communication).

A phase II study to evaluate combination of hyperthermia with pre and post of chemotherapy of sarcoma showed an impressive 5-year survival.[10]

Earlier randomized trials reported in United States had a negative outcome. A closer analysis revealed that heating techniques adopted in those studies were inadequate. There are nearly 24 randomized studies reported to which 18 have reported a positive benefit in combining hyperthermia with radiation. Patients with cervical nodes were randomized to radiation alone to a dose of 64-70 Gy and radiation with hyperthermia. Hyperthermia was delivered twice a week. The initial response was reported to have improved from 41% to 83% with a 5 year overall local control increasing from 245 to 69% and survival from none to 53%[9].

Addition of hyperthermia to radiation in cancer of cervix was reported to have improved outcome as compared to radiation alone[11]. This report by Datta et.al. was followed by a large Dutch study which also demonstrated a substantial improvement in outcome following hyperthermia. No additional toxicities were reported in this study[12].

Table - 1: Randomised Trails showing benefits with HT

Ref. No.	*Tumour*	*Treatment*	*Patients (lesions)*	*End Point*	*Effect with HT*	*Effect without HT*
11,14	Lymphnodes of head & neck tumours	RT	41(44)	CR rate 5 yr local control 5 year survival	83% 69% 53%	41% 24% 0%
15	Melanoma	RT	70(138)	CR rate 2 yr local control	62% 46%	35% 28%
16	Breast	RT	306	CR rate	59%	41%
17	Rectum	RT, surgery	115	5 year survival	36%	7%
18	Cervix	RT	64	CR	55%	31%
19	Cervix	RT	40	CR	85%	50%
20	Rectum	RT	14	Response	100%	20%

VI. INDIAN EXPERIENCE

Hyperthermia in India has not been an option that has been popularly pursued. Dr Datta's group in PGI Chandigarh, and Dr Shanta in Adiyar Institution pursued hyperthermia in the clinics in 80's. Datta reported a substantial benefit of adding hyperthermia to radiation in cervical cancer. Hyperthermia in India is now pursued actively at Nanavati Hospital, Mumbai. A modified Thermatron operating at 8.2 MHz has been installed since 2 years. Patients with head and neck cancer, cancer of cervix, oesophagus and breast, have undergone hyperthermia and radiation.

Table II shows the initial response in head and neck cancer as well as cancer of cervix. Detailed analysis of the historical data is awaited. A group of patients with head and neck cancer treated with once a week of hyperthermia have shown a very high initial response. A randomized trial to assess hyperthermia in the treatment of head and neck cancer is going to be started.

Table II - Initial Experience with Hyperthermia

	CR	*PR*	*Treatment Incomplete*
Once/wk H & N Ca (n=40)	72.5	22.5	5
Twice/wk H & N Ca (n=46)	41.3	43.47	15.21
Ca. of cervix (n=14)	57.14	21.42	21.42

VII. CONCLUSION

Hyperthermia is an important adjuvant to radiotherapy and chemotherapy. Improvement in technology has rendered it possible to heat tumours more effectively. Heating deep seated tumours effectively still remains an unsolved technical problem. Hyperthermia may find additional indications in gene therapy, stem cell purging, drug targeting with heat sensitive liposomes and potentiation of immunity in HIV. Hyperthermia as modality needs a greater exploration in many more centers in India.

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