THERMORADIOTHERAPY WITH CURATIVE INTENT - BREAST, HEAD AND NECK AND PROSTATE TUMORS

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Abstract
Purpose: To evaluate the effectiveness of hyperfractionated thermoradiotherapy (HTRT) in patients suffering from early stage cancers of the breast, head and neck and prostate that refuse conventional radiation surgery or chemotherapy. Response rates and survival were determined using objective end points. (MRI, MRS, PET scan and tumor markers).

***Material and Methods*:** Fractionation used involved daily hyperthermia treatments in conjunction with each radiation fraction. Radiation daily doses are progressively decreased from 180 to 100 cGy resulting in protracted treatment time that decreases the isoeffect biological equivalent dose by 15% to 25%. This decrease is compensated by the increased number of hyperthermia fractions which potentiates each radiation dose. Treatment is continued until an objective complete response is attained, or failure determined. 40 breast patients, 17 head and neck and 15 prostate patients were treated with a follow up of two to five years. All patients were early stage (III-a or less).

Results: Complete response rates were 82% for breast patients, 88% for head and neck and 93% for prostate patients. Projected 5 year survival rates were 80% for breast patients, 88% for head and neck, 87% for prostate patients. Side effects were less than with curative radiation therapy alone. No Grade IV toxicity (Common Toxicity Criteria) was observed.

***Conclusion*:** Protracted hyperfractionation of daily thermoradiotherapy decreases the side effects of radiation therapy, allows treating to effect using objective end point parameters, accomplishes a high percentage of complete responses and a high 5-year survival rate in the 80-90% range in early superficial tumors. It can be considered as potentially curative in Stage I-II breast, head and neck and prostate cancer when used and researched as such.
Keywords: *Cancer, head and neck, breast, prostate, hyperthermia, radiation, survival*

Introduction

That hyperthermia potentiates radiation therapy has been proven in malignant cancers, metastatic nodes in the head and neck region [1-6] and several other locations [7-9]. Due to these early findings, clinical applications were limited to recurrent advanced or metastatic cancers [10-12]. However, prospective randomized trials in the 1990's demonstrated the effectiveness of thermoradiotherapy not only in superficial tumors but also when deeper structures are affected [13-14] provided these tumors can be effectively heated. The addition of heat roughly doubles the effectiveness of radiation, but also the fact that hyperthermia increases tumor oxygenation [15-16, 41] makes hypoxic tumors such as sarcomas or glioblastomas more susceptible to thermoradiotherapy [17].
In previous publications [18] we described a treatment regimen based on protraction of the radiation fractionation combined with daily hyperthermia treatments coinciding with each radiation dose. This regimen is effective in eradicating tumors with diminished toxicity.
Based on our early experience as well as the vast literature available, we undertook to treat accessible tumors "de novo" with curative intent in a subgroup of patients that explicitly refused other accepted cancer treatment modalities, including classic radiation therapy, surgery and chemotherapy. The areas chosen were breast, head and neck and prostate cancer.

Material and Methods

1.*Hyperthermia Equipment and Technique* - Hyperthermia treatments were delivered using either microwave or ultrasound FDA approved equipment. Microwaves were delivered using a BSD-1000 machine with an MA-100 applicator at 600 MHz (BSD Medical Corporation, Salt Lake City, Utah) or a Cheung Laboratories Machine (Columbia, MD) operating at 915 MHz using its air cooled applicators. Temperature measurements were done using disposable micro thermocouple pairs (150 micron size sensors) (DANBI, Inc., Los Angeles, CA) inserted through a 20 gauge plastic catheter placed in the tumor region, providing at least 3 different measuring points. Another probe is placed on the skin above. Temperatures were recorded using P.C. computers connected to the thermocouples through an Omega Engineering temperature acquisition board. Ultrasound hyperthermia was induced using a Labthermics machine (Labthermics, Champagne, IL) using appropriate applicators (large - 15 cm x 15 cm, 3MHz and 1 MHz; small-7.5 cm x 7.5 cm,3Mhz and 1 MHz), and the same thermometry devices as described above. Breast and head and neck tumors were treated either with microwave or ultrasound. Prostate tumors using ultrasound only.

2.*Hyperthermia Fractionation and Treatment Plan* - Hyperthermia treatments of one hour each were delivered daily, 5 days/week for 16 to 20 weeks, to the tumor and involved nodal areas, within one hour of each radiation fraction. Hyperthermia was given either before or after radiation. The treated area was divided into 2 or more adjacent fields sequentially treated. Most patients received 2 daily heat treatment, one to each field. The target temperature was 41.5^o C, usually achieved at least in 2 of the measurement points. Temperatures were heterogeneous within the tumors. The hyperthermia part of the protocol extends the number of heat treatments to correspond to the number of radiation fractions, as each hyperthermia treatment precedes or follows each radiation treatment. The number of hyperthermia treatments therefore varies from 25-50 per course for each treatment field.

3.*Radiation Therapy Technique* - Radiation therapy was delivered using a Mevatron 12 Siemens machine (Siemens Medical Solutions USA, Inc., Malvern, PA) operating at 10 MeV. Tumors were treated to primary and lymph drainage areas using standard treatment plans for each of the treated tumors; and accepted quality assurance procedures.

4.*Radiation Therapy Fractionation* - The radiation protocol consists of progressively decreasing daily doses of radiation therapy combined with the daily hyperthermia treatments. Typically the treatment is started at a daily dose of 180 cGy gradually reduced to 100 cGy protracting a typical radiation therapy treatment course from 5000 cGy in five weeks to 5000 cGy given in over eight weeks or 7000 cGy in seven weeks to 7000 cGy in 14 weeks. (See Table 1) According to the ELLIS TDF formula ([19] this results in a 15% or 25% reduction of the effective radiation dose. The total dose is of course adapted to the clinical situation. To this effect, the use of objective end result parameters is introduced, including MRI, MR Spectroscopy [20], PET Scanning,

Table 1. Radiation Therapy Fractionation
Conventional Fractions

200 x 25 = 5,000	TDF = 82	35 x 200 = 7,000	TDF = 115

Protracted Hyperfractionation

[cGy]	TDF	[cGy]	TDF
180 X 10 = 1800	28	180 X 10 = 1800	28
150 X 10 = 1500	21	150 X 10 = 1500	21
120 X 10 = 1200	15	120 X 10 = 1200	15
100 X 5 = 500	6	100 X 10 = 1000	11
		50 X 30 = 1500	12
35 Fx = 5000	70	70 Fx = 7000	87

Tumor Markers and PSA levels. Typically, the treatment is continued with further reduced doses until all the objective parameters confirm a complete response or failure is determined. Therefore, as opposed to classic radiation therapy, patients are treated to effect as objectively demonstrated, instead of to a pre-determined radiation dose or number of fractions.
5.*Patient Populatio*n - Tumors Treated. - Patients included in this study belong to a subpopulation that refuses all standard medical treatments, including clinical radiation therapy, surgery and chemotherapy . All signed appropriate consent forms. Only patients with early stage III or below with a potential for eradication of localized disease were included. The tumors chosen were breast, head and neck or prostate cancer confined to an anatomical location allowing for accessible technically feasible heat delivery.

Statistics
All tests were done with Graph Pad Prism 4 software (Graph Pad Software Inc., San Diego, USA) using the method of Kaplan and Meier.

Results
Complete response rates were gratifying when compared with published results of thermoradiotherapy or our previous experience [6, 13, 21-26]. Breast tumors showed a complete response rate (CR) of 82% with 7% partial responders (PR). (See Table 2) The CR rate for head and neck tumors was 88% (See Table 3) and for prostate tumors 93% (See Table 4)

Table 2. Response Rate of Breast Cancer Patients

# of Pat.	Response		Recurrence	Dissemination	Survival
	Complete # [%]	Partial # [%]	# [%]	# [%]	# [%]
40	33 [82]	7 [18]	6 [15]	11 [27]	32 [80]

#: Number of patients
Recurrence rate was low when complete response was achieved. For breast cancer it stood at 6% (Table 2), for head and neck tumors 13% (Table 3) and at 14% for prostate tumors (Table 4).

Table 3. Response Rate of Head and Neck Cancer Patients

# of Pat.	Response		Recurrence	Dissemination	Survival
	Complete # [%]	Partial # [%]	# [%]	# [%]	# [%]
17	15 [88]	2 [12]]	2 [12]	2 [12]	15 [88]]

Dissemination rates were comparable. They were 23% for breast tumors (Table 2)13% for head and neck (Table 3) and 14% for prostate tumors (Table 4)

Table 4. Response Rate of Prostate Cancer Patients

# of Pat.	Response		Recurrence	Dissemination	Survival
	Complete # [%]	Partial # [%]	# [%]	# [%]	# [%]
15	14 [93]	1 [7]	2 [14]	2 [14]	13 [87]

Projected 5 year survival rates are depicted in Tables 5 and 6. They are 80% for breast patients, 88% for head and neck and 87% for prostate patients. Side effects were commensurable with the biological equivalent of radiation doses given. Dermatitis and occasional thermal burns (61% of treatments in breast patients). Nausea, vomiting and occasional diarrhea and cystitis when treating pelvic fields in prostate patients; mucositis, thickness of saliva and altered taste during head and neck treatment. Hyperthermia did not seem to add to the radiation early effects. In all, the treatment was well tolerated on the vast majority of the patients.

Table 5. Percentage Survival Overtime
Breast, Head and Neck, and Prostate

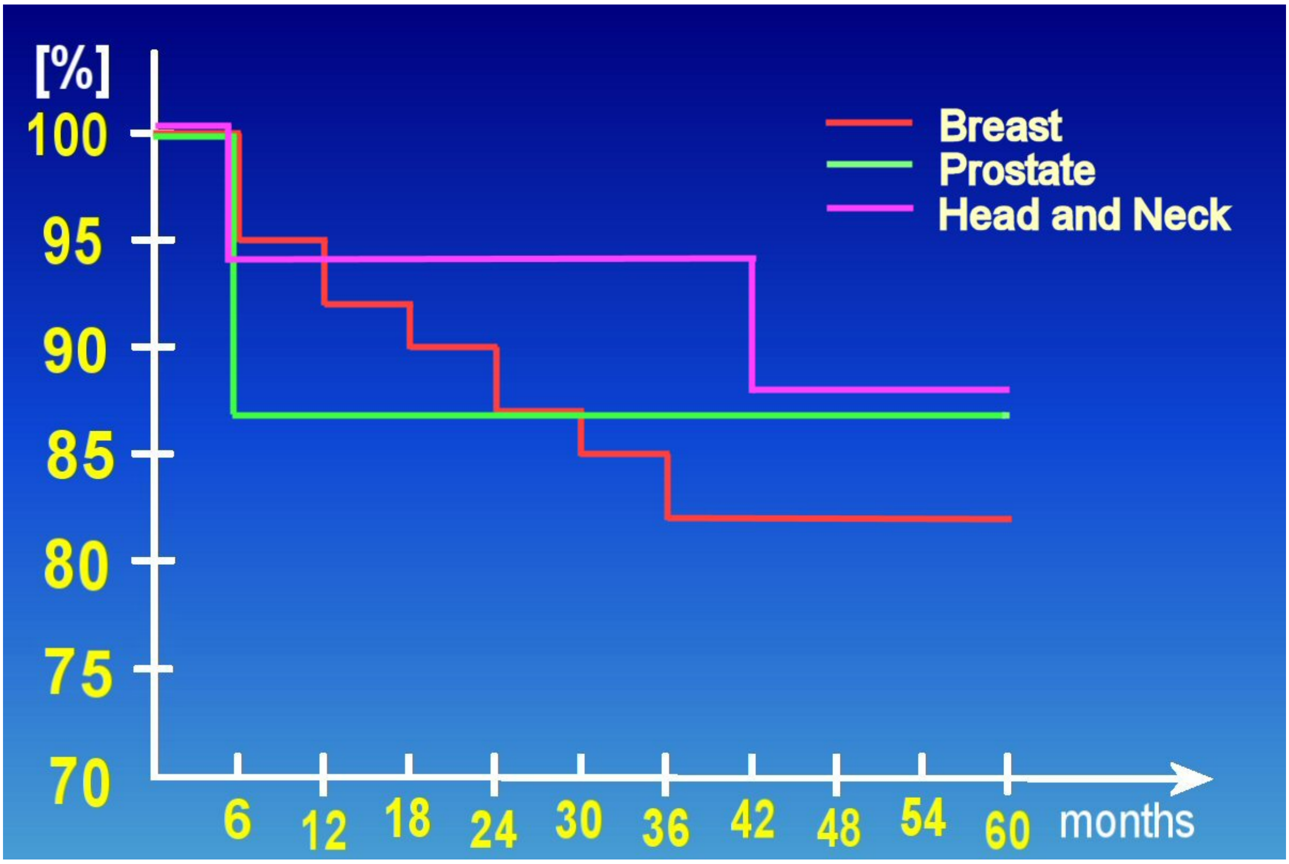

Table 6 - Five Year Overall Survival Rates

Head And Neck	88%
Prostate	87%
Breast	80%

Discussion:
Perhaps the most notable advantage of the daily hyperthermia fractionation regimen combined with diminishing radiation fraction size is that treatment may be continued until an objectively documented response (tumor markers, MRI or CT and PET scan) is obtained. This approach eliminates the "damp and pray" paradigm of classic radiation therapy for a more benign, but potentially more effective way to eradicate early stage reachable tumors. By using this approach in this study we achieved a high degree of documented complete responses with much less toxicity than that observed when using high doses of radiation. This is particularly remarkable in head and neck tumors. None of our patients required gastric intubation and only two required feeding tubes.

In spite of good clinical results the question arises of the role of thermotolerance (TT) in the proposed treatment regimen. TT is a well recognized phenomenon [27-28,31] diminishing the effectiveness of successive hyperthermia treatments in cells in vitro or in vivo in experimental animals [29-30], after a first priming heat dose. This protection to the cell kill elicited by a second heat dose seems to last 43 to 72 hours, and is the basis for the twice a week hyperthermia regimen practiced in most hyperthermia clinics.

However, several arguments can be raised to explain the good results obtained when using the daily hyperfractionated regimen in present results as well as in previously reported direct comparisons between 2 versus 5 weekly fractions when treating superficial as well as deep tumors, [22-23]. They include the following points:

(a) *Radiation eliminates thermotolerance*. The development of thermotolerance is much less or does not occur at all if each heat treatment is directly preceded by an x-ray dose, as reported by Streffer et al [32-33] when studying the effect of thermoradiotherapy on micronuclei formation on tumor melanoma cells. These findings are in good agreement with other reports in the literature [34].

(b) *Chronic thermotolerance is not expressed in many human cells.* Studies by Mackey et al [35-36] clearly demonstrated lack of development of chronic thermotolerance in several lines of normal and transformed human cells, including He La S_3 and Molt-4 lines. The clinical work of Machovsky, [37-39] who obtained outstanding regression of tumors in patients suffering from glioblastoma multiformes treated with interstitial hyperthermia alone continuously for periods of 90 hours or more also negate a role for TT in the clinical setting, for TT presence would off negated any effectiveness for the prolonged treatment, which in concept is similar to our protracted hyperfractionation. It should also be noted that Hornback et al accomplished excellent clinical results when using daily hyperthermia fractions [11].

(c) *Low pH negates thermotolerance*. In previous publications [15, 40] we demonstrated a lowering of intratumor pH following hyperthermia treatments, a finding since confirmed [40-41] in different experimental settings [33]. Streffer, Leeper, et al [42] and Gerwick et al [43, 44] demonstrated that under low pH conditions, the phenomenon of thermotolerance is greatly diminished or absent. The microvascular changes associated with hyperthermia that lead to the pH drop [45] should then be considered of importance in the clinical setting.
(d) *Reoxygenation*. Another metabolic consequence of the hyperthermic induced microvascular changes are fluctuations in the level of tissue oxygenation, as we described early on and has since been confirmed [15, 46]. As tissue temperature rises, there is a rise in T_p O_2, which peaks at about 42^{o}C and is followed by a decrease in oxygenation. 42^{o}C is then considered the tumor microvascular breaking point and is lower in tumors than in normal tissues [15, 41]. Since in real clinical practice the tissue temperatures obtained seldom exceed 41.5^{o}C when using externally induced heating, we are operating in the hypermic, hyperoxic phase and increases in T_p O_2 has indeed been documented during hyperthermia treatments [47-48]. These facts have led Song et al [46] to propose that reoxygenation may be the main mechanism for the hyperthermic potentiation of radiation induced cell kill, as ionizing radiation is more effective in oxygenated cells [17]. The elevated oxygen levels in human tumors have been demonstrated to last upwards of 24 hours [47], again justifying the effectiveness of daily hyperthermia treatments.

The potentiation of radiation by the addition of heat treatments has been extensively demonstrated, both experimentally and in clinical studies [1-14]. Early patient studies were mainly done in recurrent nodes in chest wall or neck locations [1-3, 5, 11] as well as cutaneous deposits of malignant melanoma or lymphoma [7, 23]. Since most of these recurrences followed failure of high dose radiation, hyperthermia was combined with low dose radiation. In general the responses were better with heat and low doses of radiation than with mega doses of radiation alone [6, 23]. Recent publications by Valdagni, [6] and Weltz [49] reported high percentage of long term survival for recurrent breast and head and neck tumors, respectively. Based on these early results and our own experience [8-9, 21-23, 30] as well as several prospective randomized trials proving the safety and efficacy of thermoradiotherapy [13-14, 24] we undertook to treat "de novo" a subpopulation of patients that refused conventional treatment.

The current results are gratifying and compare well with prior thermoradiotherapy literature when treating recurrent tumors - a strong correlation seems to exist between the total radiation dose complete response and tumor control rate. Perez and associates [51] reported a 40% complete response rate in patients who received less than 32 Gy compared with 67% for patients who received 32 to 40 Gy. Valdagni and colleagues reported no complete responses with doses of 10 to 29 Gy, 50% with 30 to 39 Gy, and 67% for 44 to 49 Gy. [6].
In studies of locally advanced neck disease (no prior irradiation) reported by Valdagni and colleagues [6]] and Datta and co-workers.[50] both of which used conventionally fractionated

irradiation (64 to 70 Gy in Valdagni and 60 to 65 Gy in Datta). Hyperthermia was administered twice weekly. Both studies showed an improved complete response with hyperthermia (82.3% versus 36.8% Valdagni and 55% versus 31% Datta). It was associated with improved long-term freedom from relapse in both studies. In a recent publication Valdagni [6] estimated the probability of 5-year survival in patients receiving thermoradiotherapy for stage IV recurrent neck nodes at 53.3%, versus 0% for patients treated with radiation alone. Similar 3-year survival was recently reported by Welz et al [49] when treating recurrent chest wall disease in breast cancer. The 3-year survival rate was 85% and disease free survival rate 69%. Recent publications by Kaplan et al [52], Anscher et al [53] and, Kalopurakal et al [24] described a high percentage of complete responses and long survival when combining external radiation therapy with local hyperthermia in treating advanced or recurrent adenocarcinoma of the prostate. Of particular notice is a paper by Algan et al [26] that reports a 5-year 0S (overall survival) of 73%, with a median survival of 88 months in similar cases. The safety and efficacy of thermoradiotherapy has been often proved, but a reluctance still exists to make the modality part of the initial treatment plan even in patients with tumors that are technically easy to heat. Relegating the role of such a promising and relatively less toxic modality runs counter to the wishes of patients and the hopes of oncologists. Our results open the possibility of abandoning the old paradigm of using thermoradiotherapy only on advanced or recurrent tumors doomed to long term failure by definition, and use it in early cases where its true value in the oncology armamentarian could eventually be established.

Conclusion: **Protracted hyperfractionation of daily thermoradiotherapy**

- Decreases the radiation dose by 15 to 25%
- Decreases the side effects of radiation therapy
- Allows treating to effect using objective end point parameters (tumor markers, PET scans, MRI, etc.)
- Accomplishes a high percentage of complete responses in superficial tumors
- Accomplishes a high 5-year survival rate in the 80-90% range in early superficial tumors
- Is potentially curative in early stage breast, head and neck and prostate cancers

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