CLINICAL USE OF REGIONAL HYPERTHERMIA

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For cancer control rates to significantly improve, increase in complete local control of the primary tumor is an important factor(1) . That distant metastasis can originate from uncontrolled local tumor cells has been repeatedly demonstrated, as in the results of adjuvant trials in breast cancer: Post operative radiotherapy reduced the frequency of distant metastasis equally as well as adjuvant chemotherapy. Radiation therapy proved to be actually better in post menopausal patients, including those given tamoxifen, which improved disease free survival in the chemotherapy group but not in the radiotherapy group (2).

Attempts to improve local control by giving higher irradiation dosage are frustrated by normal tissue damage, although achieving improved complete response (CR) rates as reported in the RTOG lung cancer studies,* CR with 75 Gy were 38.6%, 60 Gy 24.7%,and 50 Gy 23.1% (3). Attempts to gain therapeutic advantage by distinguishing tumor from normal tissue, primarily by altering or utilizing relative hypoxia of tumor, are ongoing (4).

Hyperthermia combined with definitive irradiation has achieved a more profound therapeutic advantage, both as to initial response and persistance of response than any other attempts at modification of standard radiotherapy. Reported long term results (5)in patients with multiple neck node metastases from squamous cell carcinoma of head and neck given 40 - 70 Gy with or without hyperthermia showed increased CR rates from 42% to 79%, a thermal enhancement ratio (TER) of 1.88. Persistance of CR at 2 years was 73 % with hyperthermia vs. 33% without. Another series also reporting results (6) in 31 patients with similar neck node

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Abbreviations used: CR=Complete Response, PR=Partial Response, NR=No response, SD=Stable Disease

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recurrence of head and neck cancer or chest wall recurrence of breast cancer indicated that tumor regression of heated lesions was more rapid than with radiotherapy alone, with at least partial response at completion of treatment in 97% of patients given hyperthermia versus 58% of controls. Recurrence rate after two year follow up was calculated to be 0.03 per lesion at risk per 6 month interval in heated areas vs. 0.2 in control areas receiving radiotherapy only. In neither study (5,6) did the addition of heat cause any increase in early or late radiation effects in normal tissue.

Other publications comparing results of hyperthermia combined with radiotherapy with the same dose of radiotherapy alone have also shown a TER of about 2. In series reported from 18 institutions throughout the world using various schedules and techniques of both hyperthermia and irradiation for over 2000 tumors of various types and sites, TER ranges from 1.16 to more than 6, with a mean of 1.88 (5 - 27, 97) (Table 1). Survival after treatment of locally recurrent tumors has been shown to correlate with sustained CR. Two to 3 years after radiotherapy alone CR was 35%, and survival 32% while after combined treatment Cr was 72%, and survival 67%(6,16).

TABLE 1. Complete Response To Irradiation (RT) Alone Versus RT And Hyperthermia (HT)

Author		Evaluable Patients	RT Alone	RT And HT
Arcangeli	(5)	163	38%	74%
Scott	(6)	62	39%	87%
U	(7)	14	14%	86%
Kim	(8,9)	238	39%	72%
Overgaard	(10)	101	39%	62%
Corry	11)	33	0	62%
Hiraoka	(12)	33	25%	71%
Li	(13)	124	29%	54%
Hornback	(14)	79	46%	72%
Shidnia	(15)	185	33%	64%
Perez	(16)	154	41%	69%
Van Der Zee	(17)	71	5%	27%
Steeves	(18)	90	31%	65%
Dunlop	(19)	86	50%	60%
Goldobenko	(20)	65	86%	100%
Muratkhodzhaev	(21)	313	25%	63%
Lindholm	(22)	85	25%	46%
Valdagni	(29)	78	36%	73%
Emami	(24)	116	24%	59%
Marmor	(25)	15	7%	47%
Gonzalez	(26,27)	46	33%	50%
Sugimachi	(97)	129	52%	80%

In other clinical studies published since 1977, the value of hyperthermia as an adjunct to radiotherapy in the treatment of superficial tumors has been affirmed (28 - 41). Hyperthermia for this purpose has been considered standard treatment since 1984. Hyperthermia has a direct cytotoxic and microcirculation effect, as well as enhancing the effect of irradiation, but results with hyperthermia alone are relatively poor with response rates of less than 60% primarily PR (11,19,39-41).

Most authors have reported no increase in acute or chronic normal tissue reaction in the radiation field with combined treatment as compared to the in same dose of radiotherapy given without hyperthermia, with the exception of thermal burns variously reported to occur in 5- 24% of treated patients. A few have found increased skin changes with combined treatment related to giving hyperthermia within a few minutes of high dose per fraction radiotherapy (43-45) or to heating normal tissue to more than 45 degrees Celsius (46).

Table 2 analyses results summarized in Table 1 to show results for the most commonly treated superficial tumors: chest wall recurrence of adenocarcinoma, neck node metastasis of squamous cell carcinoma and melanoma.

Table 2. Complete Response By Tumor Type And Site

Type - Site	References	Evaluable Tumors	RT alone	RT and HT
Chest Wall, Adeno	6,13,16,19,22,	227	33-67% (42%)	70-94% (79%)
Neck Nodes, Sq. Cell	6,20,23,42	200	22-86% (53%)	9-100% (87%)
Melanoma	5,9,15,24,26,43	575	17-57% 37%)	59-90% (68%)

Factors affecting response have been analyzed by several groups. Tumor histology does not appear to be an important factor; therefore hyperthermia is particularly indicated for treatment of radioresistant tumors such as melanoma and sarcoma. Likewise local control does not depend on tumor site, so long as adequate heating is technically feasible (35,47). Tumor size has been shown to be a significant factor undoubtedly related to limited penetration of single applicator microwave equipment (3cm at 915 MHz, 4 cm at 300 MHz) and less homogeneous heating of larger tumors. CR rates for larger tumors (over 4 cm diameter) have been found to be significantly inferior (9,12,26,42,46,47). However, for patients given full dose radiation tumor size was not significant (23). Since tumor size is also a negative prognostic factor in radiotherapy, adjunct hyperthermia appears paradoxically to be relatively more important for control of larger tumors.

Tumor response is better when radiation is increased from 20 - 30 Gy to 32 -45Gy (35,47,48,49) but not significantly further improved with full dose irradiation in the 50 - 75 Gy range as commonly given previously unirradiated tumors (35). Not surprisingly, response correlates with ability to heat the tumor. Attempts to document this relationship and in particular to establish a thermal dose based on time-temperature isoeffect have had only moderate success. Temperature measurement is still primitive, employing thermometry probes inserted in tissue which adequately track only a small portion of tumor and tumor bed. In clinical practice it is generally agreed that minimum measured tumor temperature should remain at 42 degrees Celsius for at least 30 minutes while keeping normal skin below 45 degrees Celsius, which is the temperature at which pain and thermal burns occur. Considering multiple reports, minimum tumor temperature seems to be the best predictor of response (47,49,50).

In contrast, there is no agreement as to the optimal number of hyperthermia sessions, with abundant contradictory reports. Most clinics, including our own (28,29,35) have given hyperthermia twice a week, empirically based on the well established phenomenon of thermotolerance, defined as transient increase in resistance to a second heat application. In vitro studies show decay of thermotolerance over 30 - 72 hours (51), while in vivo data suggests resistance of both normal and cancer tissue to a second heat insult may persist even at 8 - 14 days (52). Thus even with weekly treatment only the first hyperthermia session should prove fully effective. A mitigating factor is that thermotolorance persists longer in normal than tumor tissue (52,53), related to partial inhibition of thermotolerance at low pH(55). Tumors have low pH, further reduced by Hyperthermia (55).

In clinical practice the influence of thermotolerance remains unclear. Results analyzed by number and frequency of hyperthermia treatments generally ignore other factors, such as radiation dose and fractionation. For superficial tumors relation of complete response rates to number of hyperthermia have variously been reported as inverse (56,57), equal (12,58), direct (33,59,60) or ambiguous (23,29,46,61)(Table 3).

For treatment of deep tumors, analysis of results from various institutions (Table 4), one of which did a retrospective comparison of 2 per week versus 5 per week treatment (61), show a clear advantage for a greater number of hyperthermia treatment sessions (14,35,61-67)(Table 5). Several authors have stated that thermotolerance does not appear to be a significant factor in cancer treatment, based on their clinical data (47, 60, 62,68).

Deep Hyperthermia has a significant effect in combination with both radiotherapy and chemotherapy. The CR rate for deep treatment is far less than for superficial hyperthermia, with some interesting exceptions such as

Table 3

CR Rates For Superficial Hyperthermia By Thermal Dose

Author	Site/ Type	# pts/ tumor	# Treatments wk	Total	CR %
Kim (56)	Melanoma	50	1	6	74
			2	10	59
Alexander (57)	Multiple	48	1	4	42
			2	8	21
Hiraoka (12)	Multiple	40	2	2-7	50
			2	8-12	53
Kapp (58)	Multiple	38	1	2	68
			2	6	63
Luk (33)	Multiple		2	481-720min	38
			2	721+min	75
Arcangeli (59)	Multiple	23	1	5	64
			2	10	78
Leopold (60)	Sarcoma	17	1	avg.4.4	38
			2	avg.7.3	100
Bicher (29)	Multiple	121	2	8	65
Bicher (61)	Multiple	154	2	10	41
			5	25	55
Valdagni (23)	Neck	17	2	2	85
			2	6	80
Valdagni (46)	Neck	27	2	avg. 5.7	40
			3	avg. 5.7	71

Table 4

Hyperthermia For Deep Tumors

Author	Site	# pts	#tx	Response CR(%)	PR(%)
Howard (63)	Pelvis	20	1-7	1(5)	5(25)
Hiraoka (67)	Multiple	40	4-13	6(15)	19(47)
Petrovich(64)	Multiple	353	1-8	35(10)	59(17)
Shimm (65)	Multiple	44	1-7	6(14)	5(11)
Storm (62)	Multiple	960	(Avg.12)	85(9)	268(28)
Baker (66)	Multiple	107	9-15	17(16)	56(52)
Hornback(14)	IIIB Cervix	18	22-25	13(72)	
Bicher (61)	Multiple	29	10	5(17)	9(31)
Bicher (61)	Multiple	92	25	19(21)	48(52)

Table 5

Literature Summary Results

Response vs. Number of Hyperthermia Treatments

In Deep Tumors

#Tx	#Patients	CR+PR(%)	CR	PR
1 - 8	417	27 %	42	69
9 - 15	1136	41 %	113	35
25	110	73 %	32	48

definitive treatment of Stage IIIB cervix cancer (14) in which CR after irradiation alone was 48% versus 72% with combined treatment, or other deep lesions (lung, prostate, esophagus) (61). For superficial lesions (breast, head and neck) CR was also 71% (61). However, most series report a relatively poor CR rate for deep tumors probably related to the fact that most deep treatment has been for palliation in patients with bulky metastatic disease and perhaps also that heating to temperatures generally considered therapeutic has been less consistently achieved than in superficial tumors. At least 42 degrees Celsius has been obtained in 40 % (62) to 78%(63) of deep tumors in published reports that specify tumor temperature. Surprisingly response has not been shown to correlate well with minimum tumor temperature for deep tumors, CR + PR 34% at less than 42 degrees versus 38% at more than 42 degrees (64), and 69% under 43 degrees versus 53% over 43 degrees (67).

Regional deep treatment using magnetic induction (Magnetrode, Henry Medical Electronics, Los Angeles, CA.) (62) or Annular Phased Array (BSD Medical Corporation, Salt Lake City, UT) (64) has been associated with poor patient tolerance and compliance. Significant reaction (pain or systemic stress) occurs in 45% of patients treated with the currently most commonly used equipment (64). Local deep treatment using parallel opposed 300 MHz external applicators (POPAS, HBCI, Panorama City, CA) (61) has in contrast been quite well tolerated, with moderate perspiration but otherwise not different from superficial treatment.

Based on their gratifying clinical data, several authors have stated that hyperthermia treatment of deep tumors should no longer be considered investigational (61,62).

Investigation of the timing of hyperthermia and irradiation fraction indicates significant synergy at a separation of up to four hours or more(10). Although in vivo studies show maximal interaction with simultaneous treatment, two authors

have reported clinical studies comparing hyperthermia within 30 minutes of irradiation versus delay of 3-4 hours, with improved therapeutic gain using the latter regimen (43,45). While most groups have given hyperthermia following the radiation fraction , results using the reverse sequence have been similar (11,37,56).

The interaction of heat and chemotherapeutic agents has been extensively studied in vivo (69,70), since Hahn reported in 1975 that commonly used drugs show increased cell killing at increased temperatures (71). Such interaction is quite complex, however. Various mechanisms of action have been identified. Timing can be critical but differs with the agent; for instance Adriamycin and Actinomycin cytotoxicity is either inhibited or enhanced depending on when heat is applied.

The groups that compared chemotherapy alone with the same dose of the same drugs plus local or regional hyperthermia (72-75) all found significant increase in tumor response using combination treatment. No studies comparing hyperthermia alone with thermochemotherapy have been reported, and the benefit of adding chemotherapy to the hyperthermia regimen has not been established. The few reports including results in patients treated with hyperthermia combined with chemotherapy show fairly good tumor response rates but less than with hyperthermia and low dose irradiation and not clearly synergistic (60,62,76-84). Results in patients who had previously failed the same chemotherapy given without hyperthermia were equivalent to those who had not (62). Addition of immunostimulative agents to thermochemotherapy significantly increased survival (79).

Interstitial hyperthermia, employing the same implant techniques well established for endocurietherapy, has achieved higher and more uniform tumor temperatures as well as better response rates, particulary CR, than external (37,85) or intracavitary heating techniques (84). The limited published clinical experience using interstitial hyperthermia, all combined with endocurietherapy given to a total dose of 20 - 60 Gy, is summarized in Table 6 (37,85-92). All authors using interstitial hyperthermia combined with endocurietherapy agree that successful results depend on heating of the entire tumor to a minimum of 42 degrees Celsius with adequate implant geometry to include the complete tumor volume. Complications related to tumor necrosis occurred in 21% to 38 % of treatments, similar to endocurietherapy alone. Therapeutic advantage of combined treatment is suggested in comparison with historical controls (86), but no significant improvement over endocurietherapy alone has been claimed.

Preliminary results of hyperthermia for brain tumors are quite promising, safe, with palliation and surprising prolongation of survival. Three groups have used various techniques of interstitial hyperthermia alone in a total of 38 patients (93-95), while two have used external hyperthermia in 29 patients either alone (96) or with chemotherapy (97).

Analysis of hyperthermia treatment results for deep seated tumors from published data that specify site specific tumor response is shown in Tables 7,8 and 9. Tumor response rates range from 36% in the abdomen to 52% in the pelvis, but there is much wider variation among various institutions treating the same area, 18% to 71 % in the abdomen. One significant variable factor appears to be technique. In both chest and pelvis response rates have been better with intracavitary than external treatment (99, 74, 105 - 107), as also shown by Bicher (85), who found CR + PR 89% with interstitial, 87% with intracavitary, and 56% with external hyperthermia. In more recent reports, however, Bicher (61,98) has reported 78% Cr + PR in the pelvis and 74% in the chest using external treatment, most patients given daily hyperthermia for five weeks.

Table 6

Interstitial Hyperthermia Tumor Response

Author	# treated	CR
Oleson (37)	52	38%
Puthawala (86)	43	86%
Cosset (87)	23	83%
Emami (88)	48	52%
Bicher (89)	9	78%
Surmit (90)	12	48%
Vora (91)	16	68%
Lam (92)	31	61%

The vast majority of hyperthermia treatment has been for previous treatment failure or metastatic disease. The few reports of primary external treatment for locally advanced cancer are quite promising, with complete local control in the 70% - 80 % range for both superficial lesions, as previously mentioned, and for deep seated primaries of cervix (14) and lung (67,98). For pancreatic primaries complete control is rare, but significant tumor regression with prolonged survival has been achieved by hyperthermia combined with radiotherapy or chemotherapy (79,101).

Table 7

Hyperthermia For Intrathoracic Tumors

Authors	Site	Technique	#	CR	PR	SD	CR+PR
Bicher (98)	All	External	39	10	19	4	74
Storm (62)	Lung	External	147	9	38	57	32%
Baker (66)	All	External	10	0	7	NS	70%
Sugimachi (99)	Esoph	Intracav	25	6	14	NS	80%
Petrovich (100)	All	External	19	2	4	7	32%
TOTAL			240				45%

Table 8

Hyperthermia For Abdominal Tumors

Authors	Site	#	CR	PR	SD	CR+PR
Bicher (101)	Pancreas	14	1	9	2	71%
	Liver	36	4	13	8	47%
Petrovich (100)	Liver	28	1	12	8	46%
	Other	62	2	30	8	64%
Storm (62)	Liver	304	8	51	117	19%
	Other	156	9	51	44	38%
Baker (66)	Liver	14	0	9	NS	64%
	Other	17	0	5	NS	29%
Sapozink (102)	All	28	0	5	NS	18%
Moffat (78)	Liver	215	0	106	18	49%
TOTAL		874				36%

Table 9

Hyperthermia For Pelvic Tumors

Authors	Site	Technique	#	CR	PR	SD	CR+PR
Bicher (61)	All	External	32	9	16	5	78%
Petrovich(100)	All	External	55	4	33	13	67%
Storm (62)	All	External	156	17	60	56	49%
Baker (66)	All	External	28	1	19	NS	71%
Sapozink (103)	All	External	39	5	14	NS	49%
Howard (63)	All	External	20	1	5	6	30%
Steindorfer(104)	All	External	15	2	6	4	53%
Shimm (65)	All	External	32	5	3	NS	25%
Hornback (14)	Cervix	External	18	13	NS	NS	72%
Kubota (105)	Bladder	External	33	14	10	NS	73%
Szmigielski(106)	Prostate	Intracav	15	3	5	NS	53%
Yerushalmi(107)	Prostate	Intracav	32	14	13	NS	84%
Fujiwara (74)	Vagina	Intracav	42	6	22	10	67%
TOTAL			517				52%

Stable disease is an important tumor response category, not only because most of these patients have significant palliation and subjective improvement, but also because many tumors that fail to regress and are subsequently resected are found to contain no viable cancer cells (108).

The phenomenon of abscopal response with hyperthermia treatment has been specifically noted by two groups (106,109). Of 3 patients with bone metastasis who responded to intracavitary hyperthermia for locally progressive prostate cancer and followed at least one year, 2 showed complete disappearance of lesions documented by bone scan after 12 and 18 months(106). Several patients with melanoma locally recurrent in a limb as well as metastatic showed complete regression of all lesions following heated chemotherapy perfussion of the limb (109), with disease free survival at follow up for up to 15 years. Abscopal response presumably is related to stimulation of immune response, which has been demonstrated to occur after hyperthermia treatment (109).

The future of hyperthermia in cancer treatment appears most promising and exciting, but this has been true for years and

progress has been frustratingly slow. Most hyperthermia is still given at university centers. While there is a clear need for further well designed and well conducted prospective controlled clinical trials, hyperthermia needs to be more widely utilized in community oncology practice. Further research and development of hyperthermia equipment and thermometry is also needed; but current imperfect techniques of hyperthermia treatment provide significant clinical benefit.

Clinical data available now, as discussed herein, have established hyperthermia as safe and effective for tumors at any site, even including the brain. There should be no trepidation in using hyperthermia for treatment of any malignant tumor. Specific indications for hyperthermia are summarized in Table 10; but simply stated, hyperthermia is appropriate treatment for any patient with cancer unlikely to be adequately controlled by the other standard modalites - radiotherapy, surgery or chemotherapy.

Table 10

Indications For Local/Regional Hyperthermia Combined With Best Available Chemotherapy Or Irradiation

A. Local Failures Or Recurrence
   1. Breast, Chest Wall, Bone (Lung Liver)
   2. Head and Neck
   3. Skin (Advanced Basal Cell)
   4. Perineal

B. Regional Failure Or Recurrence
   1. Pelvis
   2. Neck
   3. Mediastinum

C. Metastasis
   1. Lung, Pleura
   2. Liver
   3. Bone (With Chemotherapy-Avoids Excessive Radiation To Marrow)

D. Advanced Stage Primaries (III Or IV)
   1. Head and Neck
   2. Esophagus
   3. Pelvis (Colon - Uterus - Cervix - Bladder - Prostate)
   4. Pancreas
   5. Stomach
   6. Breast (Including Inflammatory)
   7. Brain (Superficial Tumors)

E. Special Histology
   1. Melanoma
   2. Sarcoma
   3. Adenoidcystic Carcinoma

F. Patient Refusal Of Other Modalities

Only about 10% of our patients have previously untreated advanced primary disease (61), yet it is for these patients where hyperthermia can have the greatest impact on disease free survival. Future clinical trials will hopefully evaluate the potential benefits of adding hyperthermia to the treatment regimen of stage I and II malignancies. It is not unlikely that thermoradiotherapy will be shown to improve disease free survival for those patients as well as for those afflicted with more advanced disease.

Hyperthermia in the 1990's will undoubtedly become an accepted cancer treatment modality, widely used in community pratice, while research will continue at university and specialized centers. The main obstacle to accomplishing this objective is education, both of oncologists and medical specialists, as well as the patient population, which anxiously awaits the introduction of less toxic, scientifically developed effective cancer therapies. Hyperthermia has been all that, and will occupy its place in the next decade.

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