April 27, 1994

HYPERTHERMIA REVIEW OF LITERATURE

BSD MEDICAL CORP.
GUIDELINES FOR USE

The following summary includes an abbreviated review of published, prospectively randomized, clinical trials and scientifically sound studies on the role of hyperthermia as an adjuvant therapy to radiotherapy for the treatment of malignant disease. There are over 3000 published papers in the BSD hyperthermia library on all aspects of hyperthermia treatment which are available upon request.

A. HYPERTHERMIA RATIONALE

The basic premise for the addition of hyperthermia to radiation therapy is to increase local tumor control without an increase in damage to healthy tissue. About one third of all cancer deaths are caused by lack of local tumor control. Thus, an improvement in local control frequently results in a subsequent increase in disease-free survival time. Radiation is a major therapy for the treatment of local-regional disease and is effective against most solid tumors. However, tumor control often cannot be achieved without using a radiation dose which causes unacceptable damage to surrounding normal tissue, limiting the potential usefulness of radiation. Clinical studies have demonstrated that hyperthermia increases the effect of radiation on tumors to a significant degree without increasing the damage to normal tissue.

B. STUDIES

Daniel S. Kapp, Ph.D., M.D., presented a workshop, "Clinical Indications for Local Regional Hyperthermia (HT) As an Adjuvant to Radiation Therapy (XRT)"[1], [2], reviewing the studies on hyperthermia over the past decade as a Refresher Course at an American Society for Therapeutic Radiology and Oncology Meeting. Data for that workshop was developed to serve as a guideline for clinical use of hyperthermia. We have included a detailed review of this article as it provides a comprehensive clinically based overview of hyperthermia with a focus on indications for use of hyperthermia. The article provides an overview of the clinical studies relevant to a decision to use hyperthermia to treat a particular site and disease and guidelines for hyperthermia treatment based on the studies done on this modality. Dr. Kapp modified and updated previous site and disease selection recommendations for hyperthermia based on the increased "hands-on" clinical experience with this therapy, the increased understanding of the thermal distributions which can be obtained, and the toxicities encountered by hyperthermia researchers. (Dr. Kapp is on the staff of the Department of Therapeutic Radiology at Stanford University School of Medicine and is one of the leading clinical researchers in the field of hyperthermia. This work was supported in part by grants from the Public Health Service and from the National Cancer Institute.)

---

1. D.S. Kapp, “Clinical Indications for hyperthermia.” A Categorical Course in Radiation Therapy: Hyperthermia. 73rd Annual Radiological Society of North America Meeting, 1987; 77-91.

2. D.S. Kapp, “Site and disease selection for Hyperthermia clinical trials.” Int. J. Hyperthermia, 1986; 2:139-156.

The major issues in determining clinical indications for hyperthermia are the ability to deliver energy to the tumor with available equipment and the expected cure and/or local control rates for radiation therapy alone. Thirty percent [30%] of patients with cancer die because of a failure to obtain local tumor control. Researchers at Stanford evaluated the use of adjuvant hyperthermia in relation to the percentage of local failures. [1],[3] Toxicity, both in cancerous tissue and in normal tissue, was a factor in their analysis, They determined that superficially located metastatic, recurrent, or locally advanced malignancies are excellent areas for adjunctive use of hyperthermia and that, "…recurrences in previously irradiated fields can often be controlled adequately with hyperthermia in conjunction with low to moderate doses of radiation." Based on clinical research and studies, the authors recommended the use of hyperthermia for the sites discussed below.

The retreatment of recurrent chest wall metastases in previously irradiated sites with hyperthermia in conjunction with low to moderate dose radiation therapy has improved the control rate of approximately 40-50% with radiation therapy (with or without chemotherapy) to complete plus partial response rates of 90-100% when hyperthermia was added. [4],[5],[6] Duration of local control has been improved in patients treated with hyperthermia and radiation therapy when compared with historical controls [6] and when compared with concurrent controls.[7] Excellent local control rates have also been observed in previously untreated chest wall and regional modal metastases.[7] Dr. Kapp states that hyperthermia may also be indicated for use with full-dose radiation in the treatment of surgically inoperable locally advanced primary breast cancers.

Radiation therapy and adjuvant hyperthermia can be used to treat patients with advanced lymph node metastases from cancers of the head and neck, particularly patients with large (greater than 6 cm) or fixed neck nodes or with extra capsular spread of tumor into extra lymphatic soft tissue. Patients with advanced cervical nodal metastases from head and neck cancers who have not previously been treated may be good candidates for adjuvant

---

3. H.D. Suit, "Potential for improving survival rates for the cancer patient by increasing the efficacy of treatment of the primary lesion." Cancer, 1992; 50:1227-1234.

4. P. Hofman, J.J.W. Langendijk and J. Schipper, "The combination of radiotherapy with hyperthermia in protocolized clinical studies." Hyperthermic Oncology. Vol. 1, Summary papers. London: Taylor & Francis, 1984; 379-382.

5. D.S. Kapp, T.V. Samulski, J.L. Meyer, et al "Metastatic breast cancer with chest wall recurrences in previously irradiated areas: management with low-moderate dose irradiation therapy and hyperthermia." Presented at the 33rd annual meeting of the Radiation Research Society, Los Angeles, California, May 5-9, 1985.

6. C.A. Perez, R.R. Kuske, B. Emami and B. Fineberg, "Irradiation alone or combined with hyperthermia in the treatment of recurrent carcinoma of the breast in the chest wall: a nonrandomized comparison." Int. J. Hyperthermia, 1986; 2:179-187.

7. R. S. Scott, R.J.R. Johnson, K.V. Story and L. Clay, "Local hyperthermia in combination with definitive radiotherapy: increased tumor clearance, reduced recurrence rate in extended follow-up." Int. J. Radiat. Oncol. Biol. Phys., 1984; 10:2119-2123.

hyperthermia. Patients with other superficially located cutaneous or subcutaneous tumors which are symptomatic of lymph nodal metastases in previously irradiated fields may also benefit from combined-modality treatment using hyperthermia and low to moderate doses of radiation. Valdagni, *et al.,*[8] showed a statistically significant improvement in complete response rates (from 37% with radiation alone using 6,400-7,000 rads to 82% with the addition of hyperthermia) from results of an ongoing prospectively randomized trial. The addition of adjuvant hyperthermia has also been shown to result in considerably improved local control rates when compared retrospectively to radiation therapy alone for similarly staged disease.[9]

Perez, *et al.,*[9] reported an increase in complete response rates from 24% for radiation therapy alone to 59% from radiation plus hyperthermia in patients with metastatic or locally recurrent primary malignant melanomas. The relapse rate within the treatment field was very low in patients who sustained a complete response to radiation plus hyperthermia. Responses were compared with historical controls from patients treated with radiation alone at the same institution. The addition of hyperthermia to radiation therapy resulted in improved complete response rates. Kapp, *et al.,*[1] states that, "The adjunctive use of hyperthermia with radiation therapy in the treatment of symptomatic cutaneous, subcutaneous, or superficial lymph node metastases from malignant melanoma would therefore appear to be beneficial."

Kapp stated that the use of hyperthermia in conjunction with radiation therapy to treat perineal metastases could also prove to be of significant benefit, particularly in patients who have received prior radiation therapy to the region.[1] Other types of tumors which could be candidates for treatment with hyperthermia and radiation include: recurrent metastatic tumors from unknown primary sites, recurrent basal or squamous cell carcinomas, and even rarer histopathologic types of cancers, such as adenocystic carcinomas and Merkel cell tumors.[10]

Kapp states that, "Prolonged local control can be anticipated in more than 80% of lesions superficially located and less than 5 cm^3 in volume when treated with hyperthermia (two to six treatments) in conjunction with conventionally fractionated low to moderate doses of radiation (2,000-3,000 rad [20-30 Gy])."[11] This treatment regimen was well tolerated even when patients had received previous treatments in the fields. There does not seem to be an obvious difference in responses due to tumor type.[12]

---

8. R. Valdagni, D.S. Kapp and C. Valdagni, "N3 (TNM-UICC) metastatic neck nodes managed by combined radiation therapy and hyperthermia: clinical results and analysis of treatment parameters." Int. J.Hyperthermia, 1986; 2(2):189-200.

9. C.A. Perez and B. Emami, "Review of human clinical data on treatment of superficial tumors with irradiation and hyperthermia." In: B.R. Paliwal, M.W. Dewhirst and F.W. Hetzel, eds. Physical aspects of hyperthermia. Medical Physics Monograph Series. New York: American Institute of Physics (in press).

10. S. Knox and D.S. Kapp, "Hyperthermia and radiation therapy in the treatment of recurrent Merkel cell tumors." Cancer, 1988; 62(8): 1479-1486.

11. D.S. Kapp, "Areas of need for continued phase II testing in human patients." Biological, Physical and Clinical Aspects of Hyperthermia, AAPM, 1988; 424-443.

Kapp provided a review of the use of interstitial hyperthermia and radiation to treat advanced or recurrent cancer. Three trials were reviewed which demonstrated "excellent preliminary results in terms of local tumour control". An overview of these studies is provided in Table 1.

TABLE 1 INTERSTITIAL HYPERTHERMIA AND RADIATION: CLINICAL RESULTS

AUTHORS, INSTITUTION, YEARS OF STUDY	SITES	NO. OF PATIENTS	CR %	PR %	NR %	FOLLOW-UP (MONTHS)
Aristizabel and Oleson (1984). University of Arizona, 1970-1983	Gyn-pelvic Head and neck Colorectal Breast Other Total	36 9 9 3 7 64	38	39	23	8 (mean)
Emani et al. (1984) Mallinckrodt Institute, 1981-1983	Head and neck Breast Lymphoma Gynaecological Total	22 5 2 2 31	62†	21†	17†	6-30
Cosset et al. (1985) Institut Gustave-Roussy, 1981-1984	Cutaneous or subcutaneous mets Head and neck: Cervical mets Recurrent oral Cavity Skin Total	15 6 2 6 29	83‡	17‡	0‡	2-18

†Of 29 evaluable lesions.
‡Of 23 evaluable at 2 months.
Data from Kapp (2).

Kapp indicates that the most promise for deep heating with non-invasive techniques appears to be for tumors in the pelvic region. Hyperthermia and radiation may be clinically indicated for the treatment of unresectable colorectal carcinomas, postoperative treatment of node positive colorectal cancers, and treatment of pelvic recurrences or metastases. The use of adjuvant hyperthermia in conjunction with preoperative radiation may be indicated for patients presenting with inoperable tumors in an attempt to shrink the tumor and render it resectable and decrease rate of local recurrence. Other cancers which could be clinically

12. J.L. Meyer, "The clinical efficacy of localized hyperthermia." Cancer Research, 1984; 44(suppl.):4745s- 4751 S.

indicated for treatment with radiation therapy and deep hyperthermia include cancer of the urinary bladder, carcinoma of the prostate, carcinoma of the uterine cervix and of the uterine corpus, and soft-tissue sarcomas and bone tumors. Interstitial hyperthermia may prove to be beneficial in patients with recurrent or previously untreated malignant brain tumors.

Kapp sums up his analysis by stating that, "In summary, the clinical use of hyperthermia as an adjunct to radiation therapy should be considered in situations in which (a) the probability of palliation or local-regional control is low by currently available standard treatment modalities and (b) hyperthermia can be safely administered to the tumor site."

Issels, *et al.,*[13] treated 63 patients who had high-risk, non-metastatic soft tissue sarcoma with systemic chemotherapy and regional hyperthermia produced using the BSD-2000 followed by surgery. Patients had grade II or III tumors >8crn and/or extracompartmental tumor extension (28 patients) or local recurrence (35 patients). The majority of patients had been heavily pre-treated. The areas treated included the pelvic area, trunk, or extremities. In an earlier publication[14] Isseis *et al.* provided a correlation of treatment factors with response for 40 of these patients (Table 2).

TABLE 2 CORRELATION OF TREATMENT FACTORS TO RESPONSE

	P-VALUE SINGLE VARIABLE
Age	.58
Kamofsky status	.004*
Tumor volume	.88
No. of satisfactory† heat treatments	.02
T_{min}	.03
T_{max}	.08
$T20_{mean}$	.003*
$T50_{mean}$	.006*
$T90_{mean}$	.004*
TD_{mean}	.02
TD_{min}	.007*
TD_{max}	.02

NOTE: Based on Mann-Whitney nonparametric test.
*Statistically significant (p<.01).
†Defined as having achieved intratumor Ts of greater than 43.0°C in at least one sensor locator.
Data from Issels. (14).

13 R.D. Issels, S. Rahman, M. Santl, Ch. Salat, W. Hill, K.-W. Jauch, F.-W. Hagena, K. Peter, and W. Wilmanns, "Preoperative thermochemotherapy in soft tissue sarcoma." Abstracts of the Hyperthermia in Clinical Oncology Meeting, Munich, Germany, 1993.

14 R.D. Issels, S. Prenninger, A. Nagele, E. Boehm, H. Sauer, K-W. Jauch, H. Denecke, H. Berger, K. Peter, and W. Wilmanns, "Ifosfamide plus etoposide combined with regional hyperthermia in patients with locally advanced sarcomas: a phase II study." Journal of Clinical Oncology, 1990; 8(11):11818-1829.

As of 1993, Issels reported that a total of 55 patients had undergone surgery after receiving 2-5 cycles of chemotherapy combined with regional HT, and 48 (87%) of these large tumors could be resected without amputation. Pathological evaluation was done on the tumors of the 48 patients who had surgical resection. Nineteen responders had >50% histological necrosis and/or regression, and in 7 patients a pathological complete response CR, 25 PR). Thirty-nine patients (62%) exhibited no evidence of disease after a median follow-up time of 20 months. Additional studies are currently ongoing to further confirm "the obvious potential of preoperative thermochemotherapy in regard to local control and disease free survival".

The European Society for Hyperthermic Oncology (ESHO) [15] conducted a multi-center randomized Phase III study to investigate the value of the addition of hyperthermia to radiation therapy to treat malignant melanoma. A total of 134 metastatic or recurrent malignant melanoma lesions were randomized to receive either RT alone (3 fractions in 8 days) or hyperthermia (43°C for 60 minutes) following each radiation fraction. Tumors were stratified according to size, above or below 4 cm. Lesions were randomly assigned to either 24 or 27 Gy total radiation dose. The patients had a follow-up time ranging from 3 to 72 months. The overall two year actuarial local and regional tumor control rate was 37%. Using univariate analysis, hyperthermia was statistically significant as a prognostic variable with a 46% control rate for radiation plus hyperthermia vs. a 28 control rate for radiation alone ($p = 0.008$); as was radiation with a 56% control rate for 27 Gy vs. a 25% control rate for 24 Gy ($p = 0.002$); but tumor size was not statistically significant with a rate of 42% for small lesions vs. 29% for large lesions ($p = 0.21$). The hyperthermia significantly improved the therapeutic effect of radiation therapy on malignant melanoma and did not significantly increase acute or late radiation reactions. The 2 year local/regional tumor control rate was 28% for radiation alone and 46% for radiation and hyperthermia ($p=0.008$). A stepwise logistic regression provided the significant prognostic parameters for local control shown in Table 3.

TABLE 3 SIGNIFICANT PROGNOSTIC PARAMETERS FOR LOCAL CONTROL

VARIABLE	P-VALUE	ODDS RATIO (95% c.l.)
Hyperthermia	0.005	2.98 (1.50-7.49)
Tumor size	0.002	0.81 (0.68-0.97)
Radiation dose	0.015	2.61 (1.29-6.35)

Data from Overgaard (15).

Feldmann, et al.,[16] treated 30 patients who had pelvic recurrences from colorectal cancer. The BSD-1000 and 8SD-2000 were used to deliver deep hyperthermia in

15. J. Overgaard, "Results of the ESHO (3-85) phase III study for metastatic melanoma." Abstracts of the Hyperthermia in Clinical Oncology Meeting, Munich, Germany, 1993.

16. H.J. Feldmann, K. Strehl, R. Romanowski, W. Baumhoer, and H. Sack, "Thermoradiotherapy of recurrent rectal cancer: treatment parameters and local tumor control." Abstracts of the Hyperthermia in Clinical Oncology Meeting, Munich, Germany, 1993.

conjunction with radiotherapy. Seven patients exhibited local tumor control with a follow-up period of 20 months and 3 patients had no evidence of disease with a follow-up period of 9 months. The authors stated that, "These data support activity for regional hyperthermia in combination with definitive radiotherapy in patients with advanced pelvic recurrences."

Leopold, *et al.,*[17] evaluated the predictive value of thermal parameters with regard to tumor response in superficial malignancies treated with hyperthermia and radiation therapy. One hundred eleven individual treatment fields with 1 or more tumor nodules were evaluable. The authors concluded that, ''The significance of thermal variables with regard to tumor response strongly supports the contention that hyperthermia can be a useful adjunct to irradiation for the local treatment of cancer."

Sharma, *et al.*,[18] in "A prospective randomized study of local hyperthermia as a supplement and radiosensitizer in the treatment of carcinoma of the cervix with radiotherapy," published results of treatment of 50 patients with stage II and III carcinoma of the cervix. This was a prospectively randomized study of the effect of hyperthermia as a supplement to standard radiotherapy. Failures following radiation alone are common in advanced stages of cervical cancer. Other therapies, including radiation sensitizers, adjunctive chemotherapy, and immunotherapy have been tried without success. Twenty- five [25] patients received radiotherapy alone and 25 patients received radiotherapy and hyperthermia. Both groups were followed for a period of 18 months. Toxicity and efficacy were evaluated. All patients in both groups received the same radiation therapy dose and fractionation. The hyperthermia patients received the same hyperthermia dose, 42 to 43°C for 30 minutes with an intracavitary applicator. There was no major morbidity caused by the hyperthermia, and the hyperthermia did not exacerbate the adverse reactions to radiation. Local control was better in the hyperthermia arm, particularly in large tumors, infiltrative tumors and tumors with moderately differentiated histology. The authors concluded that, "Hyperthermia in combination with radiation seems to be an effective modality in improving local control rates in advanced cases of carcinoma of the cervix."

Kapp, *et al.,*[19] published a retrospective review of the treatment of 241 fields in 89 patients who had biopsy confirmed recurrent or metastatic adenocarcinoma of the breast and involvement of the chest wall and/or regional lymph modes with diffuse or nodular metastases. Treatment was with external hyperthermia and radiation; thermal mapping and or multipoint measurement of tumor temperatures and at least one follow-up evaluation at 32 weeks or more following end of treatment were required for evaluation. The majority of patients were heavily pretreated. The researchers did a comprehensive analysis of these patients to determine patient response and tolerance and to identify prognostic factors.

---

17. K. Leopold, M. Dewhirst, Th. Samulski, R. Dodge, S. George, J. Blivin, and J. Oleson, "Predictive thermal parameters related to tumor response." Abstracts of the Hyperthermia in Clinical Oncology Meeting, Munich, Germany, 1993.

18. S. Sharma, F.D. Patel, A.P.S. Sandhu, B.D. Gupta, N.S. Yadav, "A prospective randomized study of local hyperthermia as a supplement radiosensitizer in the treatment of carcinoma of the cervix with radiotherapy." Endocurietherapy/Hyperthermia Oncology, 1989; 5:151-159.

19. D.S. Kapp, T.A. Barnett, R.S. Cox, E.R. Lee, A Lohrbach, P. Fessenden, "Hyperthermia and radiation therapy of local-regional recurrent breast cancer: Prognostic factors for response and local control of diffuse or nodular tumors." Int.. J. Radiat. Oncol. BioI. Phys., 1991; 20(5):1147-1164.

Their results suggested that complete response rates and duration of local control could be obtained by the use of maximum tolerated radiation doses, extended fields with adequate margins, improved quality of hyperthermia treatments, and the use of concurrent hormonal therapy. They stated that their studies "... confirm both the efficacy and safety of RT-HT and are in general agreement with previously reported studies."

Steeves, et al.,[20] did a matched-pair analysis of response in a controlled study with 20 patients with two or more superficial metastatic or recurrent neoplasms to compare the effect of radiation plus local hyperthermia to radiation alone, "Matched-Pair Analysis of Response to Local Hyperthermia and Megavoltage Electron therapy for Superficial Human Tumors." BSD equipment was used for this study. All patients had tumors not amenable to conventional therapy. All of the lesions in a particular patient were treated to the same dose with the same fractionation scheme. The treatment was delivered so that all of the clinically evident superficial tumor volume was irradiated; if there were multiple or large confluent lesions present, only part of the tumor volume received local hyperthermia. The controlling thermometry was uniformly placed directly underneath or in the deepest portion of each tumor.

Nine [45%] of the patients had a better response (CR and PR) in the areas that were treated with adjuvant hyperthermia as compared to radiation alone. The CR was 65% for lesions treated with both hyperthermia and radiation compared with 30% for lesions treated with the same doses of radiation alone. Nine of the 20 patients had CRs in areas receiving radiation and heat; six of these same nine patients also had CRs in areas that were treated with the same doses of radiation alone. However, three of 20 patients had a CR to hyperthermia and radiation but not to radiation alone. The difference in these three patients was statistically significant ($P < .05$). The thermal dose had a prognostic influence on the probability of tumor response to hyperthermia. Only one variable, prior radiation, was significantly associated with increased tumor response in the areas treated with radiation alone. This was an unexpected observation.

There were no instances in which hyperthermia was associated with a poorer response than radiation alone in two regions treated on a given patient. Both regions on a given patient had the same response in 55% of the patients, but 45% of the patients demonstrated a better response in the heated that in the unheated areas ($P<.005$). The authors clearly demonstrated improved tumor regression from local hyperthermia when comparing the responsiveness of superficial neoplasms of similar size. The researchers referenced other analyses by Oleson, *et al.,* Luk, *et al.,* Overgaard, *et al.,* Kim, *et al.,* Arcangeli, *et al.,* and Scott, *et al.,* which had shown a twofold increase in complete response rates of heated tumors compared to that for the unheated controls, the same response level observed in this study. There was a good correlation shown between improved response in the heated versus the unheated tumor and the thermal dose delivered. The authors indicated that the toxicity was acceptable but not insignificant. The tissue toxicity was minimal. The degree of erythema and inflammation was equivalent between the heated and unheated areas that received the same dose of radiation. There were mild thermal blisters in five patients in the heated areas. There were no cases of severe blistering, severe pain, or infection.

---

20. R.A. Steeves, S.B. Severson, B.R. Paliwal, S. Anderson, H.I. Robins, "Matched-pair analysis of response to local hyperthermia and megavoltage election therapy for superficial human tumors." Endocurietherapy/Hyperthermia Oncology, 1986; 2:163-17

Overgaard[21] reviewed the current clinical role of hyperthermia as an adjuvant to radiotherapy. The author stated that significant information has been generated about hyperthermia in recent years and that, "... there now seems to be sufficient justification for applying adjuvant hyperthermia in the primary treatment of cancer, the prime purpose being local control of bulky primary lesions." Overgaard provided a table comparing the percentage of complete responses (CR) for a series of studies which included comparable lesions which have been treated with radiation therapy alone and radiation combined with hyperthermia (Table 4). In his analysis, Overgaard stated that, "Although the number and size of heat and radiation fractions as well as the sequence and interval between the two modalities differ among these studies, a remarkable heat improvement of the radiation response has been uniformly achieved."

TABLE 4 HYPERTHERMIA AND RADIATION: PERCENTAGE OF COMPLETE RESPONSES FOR COMPARABLE LESIONS

STUDY	NO. OF TUMORS	RT ONLY % OF CR	RT + HT % OF CR
Arcangeli et al.	163	38	74
U et al.	7	14	85
Overgaard	62	34	67
Johnson et al.	14	36	86
Kim et al.	159	33	80
Bide et al.	76	0	7
Hiraoka et al.	33	25	71
Kochegarov et al.	161	16	63
Lindholm et al.	85	25	46
Corry et al.	33	0	62
Scott et al.	44	64	86
Li et al.	124	29	54
van der Zee et al.	71	5	27
Steeves et al.	75	23	61
Dunlop et al.	86	50	60
Gonzalez et al.	46	33	50
Valdagni et al.	78	36	73
Li et al.	64	36	64

Data from Overgaard (20).

Leopold, et al.,[22] conducted a phase II trial at Duke University which involved treatment of patients with Stage IIB-IVA soft tissue sarcomas with preoperative hyperthermia

---

21. J. Overgaard, "Hyperthermia as an adjuvant to radiotherapy." Strahlentherapie und Onkologie, 1987; 163:453-457.

22. K.A. Leopold, J. Harrelson, L. Prosnitz, T. Samulski, M.W. Dewhirst, J.R. Oleson,"Preoperative hyperthermia and radiation for soft tissue sarcomas: Advantage of two vs. one hyperthermia treatments per week." Int. J. Radiat. Oncol. Biol. Phys., 1989: 16(1):107-115.

plus radiation therapy. All of the sarcomas were amenable to wide local excision. Patients were randomized to one versus two treatments per week and they were stratified by tumor volume. 17 patients were treated and analyzed. Surgical extirpation was performed 4 weeks after completion of HT/RT. Histopathological examination of the resected lesions was conducted to evaluate the effect of treatment. All nine patients in the 2 hyperthermia treatments per week group had extensive histopathological changes; only 3 of the 8 patients in the 1 hyperthermia treatment per week group showed extensive changes. ($p<0.009$). This study suggested an advantage to two hyperthermia treatments per week.

Valdagni, *et al.*,[23] conducted a controlled prospective randomized clinical trial to evaluate radical adiation alone versus radical radiation plus hyperthermia for N3 metastatic squamous cell cervical lymph neck nodes, "Radical Radiation Alone Versus Radical Radiation Plus Microwave Hyperthermia for N3 (TNM-UICC) Neck Nodes: A Prospective Randomized Clinical Trial." Conventionally fractionated radical radiation to a total dose of 64-70 Gy was delivered to all patients and local hyperthermia was added to the treatment arm and delivered twice a week. Incidence of both acute local toxicity and local control rates were evaluated as the two major end points. Patients randomized to the combined treatment arm were further randomized to receive either a total of two or six hyperthermia sessions, a secondary end point being the clinical efficacy evaluation of a limited number of heat treatments. The patient population was homogeneous for disease and Stage. Patient eligibility required no previous radiation or chemotherapy to neck regions. The BSD-1000 was used to deliver hyperthermia at a frequency range of 280-300 MHz.

Thirty six nodes were evaluable when the study was closed prematurely due to ethical reasons as an interim analysis had revealed a statistically significant difference in complete response rates in favor of the combined arm ($p=0.0152$). Both arms were equivalent in average total RT dose delivered (67.05 Gy for the radiation alone arm and 67.85 Gy for the hyperthermia and radiation arm) and in average maximum node diameter (4.81 cm for the RT and 4.88 cm for the RT and hyperthermia arm). In the nodes that received radiation alone, there were 36.8% [7/19] complete responses, 42.1% [8/19] partial responses, and 21.1% 4/19] progressive disease. In the nodes that received radiation and hyperthermia, 83.3% [14/17] exhibited complete responses; 5.9% [1/17] exhibited partial responses, and 11.8% [2/17] demonstrated progressive tumor. The 45.5% difference in complete response rates between the two arms is statistically significant ($p=0.0152$). Tumor dimension was a predictor of control in nodes that received radiation only but was not predictive of control in nodes that received radiation and heat. Increasing total dose of radiation improved clinical response in the RT and hyperthermia arm but did not improve clinical response in the RT only arm. Preliminary analysis of the 2 versus 6 treatment protocol demonstrated no clear difference in local control rates between the two arms of the study. (A presentation was made by Valdagni at the North American Hyperthermia Society meeting in Tucson, Arizona, March 1993, that this sample size was insufficient to support this conclusion.)

Acute local toxicities were similar in both arms. Only one skin burn was observed. Power was adjusted due to patient pain in 15% of the heat sessions. The addition of heat did not result in any enhancement of early side effects on normal skin, with the exception of one blister which resulted from superficial overheating due to metastatic skin involvement. There was a possible treatment related death. One patient in the RT and hyperthermia arm died 2 months after therapy completion with a carotid rupture associated with extensive tumor necrosis. The patient initially presented with skin involvement by extracapsular nodal spread. He developed a 0.5 cm fistula in the neck at a site of the previous involvement. Nodal disease was locally controlled at the time of death; this patient was not included in subsequent analyses.

---

23. R. Valdagni, M. Amichetti, G. Pani, "Radical radiation alone versus radical radiation plus microwave hyperthermia for N3 (TNM-UICC) neck nodes: A prospective randomized clinical trial." Int. J. Radiat. Oncol. Biol. Phys., 1988; 15(1):13-

Valdagni, *et al.,*[21] stated that, "This study confirms and substantiates our previous finding on the ability of hyperthermia to act in conjunction with radical irradiation in improving 'early' local control of fixed N3 (TNM-UICC) squamous cell cervical lymph nodes. It also confirms that hyperthermia does not increase acute side effects in skin and subcutaneous tissues when combined with conventionally fractionated radical dose radiation." The authors stated that the published research shows that in metastatic neck nodes treated with hyperthermia and radiation therapy, early complete response is maintained in up to 92% of cases.

The Radiation Therapy Oncology Group (RTOG)[24] initiated randomized multi-institutional trials on hyperthermia in 1981. At the same time that the RTOG initiated randomized trials, NCI awarded a multi-institutional contract for the evaluation of currently available hyperthermia equipment. The concept of temperature distribution analysis, index temperatures such as T_{90}, and the QA procedures necessary to adequately deliver and evaluate hyperthermia were developed during this analysis. At the conclusion of this analysis, it was obvious that the RTOG studies which were on-going were using completely inappropriate QA and thermometry procedures and that the tumor sizes being treated during these studies were too large for adequate heating with the equipment being utilized. No measured thermometry was utilized for some patients; most patients had only one measured temperature point, procedures which were now known to produce substandard hyperthermia. The concepts which would have provided scientific validity to the RTOG studies had not been developed at the time these studies were initiated. However, a five paper series on QA methodology for HT was generated in 1981 to address these issues. The applicators used for treatment could not adequately heat tumors large than 3cm, a fact which was not detected during the RTOG trial due to the inadequate thermometry being employed. The results of the first randomized multi-institutional RTOG trial demonstrated statistically significant results for tumors <3cm, the subset of tumors which would have been heated effectively, but did not demonstrate statistical significance for the subset of larger tumors which would not have been heated effectively. Local control was improved by the addition of hyperthermia for tumors <3cm (p=0.02)[25]. The CR rate was 52% for HT and RT versus 30% for RT alone and there was a lower recurrence rate for complete responders (7% for RT alone versus 45% for HT and RT). Using the probability of recurrence (PBR) analysis, the data demonstrated that the HT and RT patients had an 82% probability of maintaining their response 12 months after treatment, as compared to 12% for RT alone (p=0.02).

---

24. M. Dewhirst, P. Corry, "Future directions for multi-institutional clinical trials in hyperthermia." A National Cancer Institute Workshop, Washington, DC, 1992.

25. CA Perez, T. Pajak, B. Emami, N.B. Hornback, L. Tupchong, P. Rubin, "Randomized phase III study comparing irradiation and hyperthermia with irradiation alone in superficial measurable tumors." American Journal of Clinical Oncology. 1991; 14(2):133-141.

Lee, *et al.,*[26] presented an article at the North American Hyperthermia Group Annual Conference in 1987, "Preferential Heating of Raised Surface Tumors with Microwaves (MW)," which examined the observation that tumors which are raised above the surface heat better. The authors had treated 40 raised tumors; 34 of these tumors had thermal profile data. The analysis and comparison of thermal parameters for raised tumors for a particular anatomical site and all tumors for that site showed no real differences except for the 15 head and neck raised tumors which did show preferential heating compared to the non-raised tumors for the group. They examined the data for all raised tumors irrespective of anatomical site. They also did this for the heating devices as a group. The results suggest an enhanced effect for the cavity MW applicators (BSD MA-150 and MA-201) as the height of the tumor above the surface increases. The authors concluded that there are indications that head and neck tumors may show a dose enhancement effect for raised tumors in microwave fields, even though this could not be confirmed. Waveguide applicators also show an increasing effect with increasing height of the tumor above the surface.

Molls, e*t al*.,[27] published an article evaluating several techniques to induce regional hyperthermia, "Regional hyperthermia - a feasibility study." Heating equipment and tolerance to treatment were evaluated at half depth, defined by the authors as greater than 3 and less than 7 cm under the surface, and at depth, defined as about 7 cm under the surface. Low radiation doses of from 20 to 30 Gy were delivered to all patients with the exception of one patient with renal carcinoma. Heat was delivered within one hour following radiation, twice or four times per week. The goal was to maintain the tumor center at 42.5°C for 30 to 60 minutes. The majority of the catheters used for temperature monitoring were inserted under CT or ultrasound control for precise data regarding tumor temperature. Thermal mapping was performed every 25 minutes after the beginning of the hyperthermia. Seventeen patients with tumors ranging from 3 to 7 cm under the surface were treated; 44% of the treatments reached temperatures of 41.5°C to 44.7°C at the center of the tumor. Complete and partial responses were observed in ten patients [60%]. There were two children treated with the BSD Applicators, a fourteen year old girl and an eleven year old boy. Both children had neuroectodermal Askin tumors in the lumbosacral region. Both patients received 50 Gy conventionally fractionated and were aggressively treated following incomplete resection. The boy was heated twice a week for a total of nine treatments and received polychemotherapy with Adriamycin, lfosphamid, Actinomycin D, and Vincristine. The girl was heated four times per week for a total of 23 treatments; chemotherapy was changed after one cycle due to resistance and was then stopped following two other schedules due to myelosuppression. Both children tolerated the aggressive treatment, and there were no additional side effects or complications. At present, both the girl and the boy are in good physical condition. There is no evidence of tumor growth at 12 months after treatment for the boy and 24 months for the girl, confirmed clinically and with CT.

---

26. E.R. Lee, P. Fessenden, D.S. Kapp, "Preferential heating of raised surface tumors with microwaves (MW)." Presented at the 7th Annual Meeting of the North American Hyperthermia Group, Atlanta, Georgia, 1987; 1-5.

27. M. Molls, H.J. Feldmann, S. Adler, H. Sack, "Regional hyperthermia - a feasibility study." Strahlentherapie und Onkologie, 1989; 165(10):717-720.

The occurrence of adverse effects was minimal. Thermal injuries were rare. One patient had a large ulceration related to hyperthermia induced tumor regression. The patient had an unresectable soft tissue sarcoma of the chest wall which disappeared rapidly after 36 Gy and six hyperthermia sessions leaving a large ulceration of the chest wall which was corrected by plastic surgery. The authors concluded that there is adequate heat deposition for treatment of surface and subsurface tumors up to 7 cm depth under the surface in different anatomical regions. Acute side effects were relatively mild.

Valdagni and Amichetti[28] reported clinical results of the treatment of 117 tumors using the BSD-1000. The protocol used required histopathologically proven malignancy and either previous failure or probable failure from the use of all other "reasonable therapeutic measures". Patients had a life expectancy of at least two months. One patient received Adriamycin three hours before and after HT. All other patients received radiation therapy appropriate to the site to be treated. Thirty patients with malignant melanoma metastasis were treated with HT and RT; 24 were evaluable. Local control was achieved in 80% of the patients who were treated with 30 Gy, five sessions, twice a week plus six HT treatments. Fifty-one patients with fixed and inoperable neck nodes were treated. There were 75% complete responders and the treatment demonstrated a "clear improvement in local control rates when hyperthermia is combined with conventional radical irradiation." Even with a median irradiation dose of 3860 cGy, a 53% complete response rate was observed. The clinical response for all patients three months after the treatment is shown in Table 5

TABLE 5 CLINICAL RESPONSE FOR ADVANCED TUMORS TREATED WITH HYPERTHERMIA

	NO. OF PATIENTS (TUMORS)	COMPLETE RESPONSE	PARTIAL RESPONSE	NO RESPONSE*
N3 squamous cell neck nodes[1]	50 (51)			
-radical RT+HT		72.7% (24)	15.2% (5)	12.1% (4)
-palliative RT+HT		53.8% (7)	30.8% (4)	15.4% (2)
Malignant melanoma[2]	21 (30)	70.8% (17)	25.0% (6)	4.2% (1)
Chest wall recurrence from metastatic breast cancer[3]	11 (12)	54.5% (6)	27.3% (3)	18.2% (2)
Sarcoma[4]	6 (8)	42.9% (3)	42.9% (3)	14.2% (1)
Miscellaneous[5]	14 (16)	50.0% (6)	25.0% (3)	25.0% (3)

*No response category includes P.D. and N.C. [1]Not evaluable: five nodes. [2]Not evaluable: six patients (five lesions >7cm). [3]One patient treated with hyperthermia + chemotherapy: one no change. [4]Not evaluable: one patient. [5]Not evaluable: four patients.
Date from Valdagni and Amichetti (27).

28. R. Valdagni, M. Amichetti, "Clinical hyperthermia: five year's experience." Strahlentherapie und Onkologie, 1987; 163(7):443-445.

Petersen, *et al.,*[29] studied the use of hyperthermia and radiation for the retreatment of superficial recurrences in Hodgkin's Disease, "Local Hyperthermia and Radiation Therapy in the Retreatment of Superficially Located Recurrences in Hodgkin's Disease." This patient received 3 hyperthermia treatments and 2944 cGy radiation for treatment of a posterial cervical recurrence. The maximum diameter of the disease was 5.2 cm. The patient achieved local control and subsequently died of unknown etiology. Her node was excised at one month following therapy. Pathology showed foci of necrosis surrounded by giant cells and chronic inflammatory cells with small foci of atypical lymphoid tissue. The tumor margins were suspicious but no local recurrence was subsequently documented. The authors concluded that seven patients with symptomatic superficial recurrent masses who had received previous radiation and multiple chemotherapeutic regimens had excellent local control following the administration of hyperthermia and radiation. Good temperature distributions were obtained without significant toxicity. They concluded that further studies are warranted and that hyperthermia in conjunction with radiation may be applicable for either palliative or cytoreductive purposes for superficially recurrent Hodgkin's disease.

Molls, et al.,[30] reported on their first results of treatment using the BSD-1000 system, "First Results After Hyperthermia Treatment with the BSD System in Essen." Twenty-eight [28] patients received 273 treatments, most for palliation of symptoms. Ten [10] patients were either still under treatment or not evaluable; thus, data was reported on 18 patients. One patient presented with a sternal metastasis of a breast carcinoma which had penetrated through the bone. Even though the radiation dose was very low (20 Gy) due to previous therapy, the hyperthermia and radiation resulted in a complete response. The authors stated that the most impressive result was a patient with a large (5 cm X 20 cm) malignant melanoma in the paravertebral soft tissue who received 15 treatments with BSD's Dual Horn applicator and 46 Gy of radiation due to the proximity of the spinal cord. The patient had very severe pain prior to treatment. Treatment resulted in a complete response and complete relief from pain. There were no acute or severe treatment-related complications. Side effects included pain, erythemas, and small epitheliolytic lesions. The tumor sizes ranged from microscopic to 20 cm; radiation ranged from 20 to 50 Gy; the number of treatments from 7 to 19; the highest temperature was 43.5°C; average time at temperatures over 41°C ranged from 10 to 20. Responses included 2 patients with complete response and 2 patients with no change. The other patients had not been evaluated for response at that time. They referenced another study by Van der Zee, *et al*., 1986, which showed a response (PR and CR) of about 80% in a large group of breast carcinoma patients with radiation doses of only 12-25 Gy. The authors indicated that palliative treatment of breast cancer with low radiation doses is a promising treatment possibility.

Van der Zee[31] presented data on studies involving reirradiation combined with hyperthermia to treat 126 recurrent breast cancer patients. CR rates from 20 to 27% have been reported for the use of reirradiation alone at the same dose range used in this study.

---

29. I.A. Petersen and D.S. Kapp, "Local hyperthermia and radiation therapy in the retreatment of superficially located recurrences in Hodgkin's disease." Int. J. Radiat. Oncol. BioI. Phys., 1990; 18(3):603-611.

30. M. Molls, W. Baumhoer, H.J. Feldmann, R.D. Muller, H. Sack, "First results after hyperthermia treatment with the BSD system in Essen." Recent Results in Cancer Research, 1988; 107:129-135.

31 J. van der Zee, G.C. van Rhoon, "Hyperthermia in clinical oncology." Strahlentherapie und Onkologie, 1991; 167:46-61

The addition of hyperthermia to this dose range produced CR rates from 37 to 88%. Using reirradiation alone with the identical schedule used in this study of 8 x 4 Gy, the RTOG 81-4 study produced CR rates of 26%, significantly lower than the CR rates of 61% achieved using 8 x 4 Gy plus hyperthermia (p=0.014). The researchers indicated that the data shows that, even using heating techniques which are not sufficient for adequate heating of a particular group of tumors, the overall CR rate is significantly higher than the overall CR rate produced using RT alone at the same dose.

C. CONCLUSIONS

Because a lack of local tumor control causes over one-third of all cancer deaths, improved local tumor control would result in an increase in survival time. Survival rates for all sites would be increased if patients did not have local failure, and local/regional control would be expected to result in a cure if no metastatic disease was present at the time of treatment. Uncontrolled local tumors can also cause severe symptoms and thus reduce quality of life and increase cost of care. Kapp[32] estimated the number of deaths caused from local control failure (Table 6).

TABLE 6 ESTIMATED IMPACT OF LOCAL FAILURE IN CANCER DEATHS IN U.S.A.

PRIMARY TUMOUR SITE	ANNUAL DEATHS 1985†	ESTIMATED LOCAL FAILURES AS MAJOR CAUSE OF DEATH‡	
		NO. OF PATIENTS	PER CENT
Brain and CNS	10,100	9,600	95
Ovary	11,600	9,700	84
Skin	7,400§	5,100	69
Prostate	25,500	15,600	61
Cervix uterus	6,800	4,100	60
Corpus uterus	2,900	1,700	59
Oesophagus	8,800	5,200	59
Bladder	10,800	5,800	54
Head and neck	9,500	3,900	41
Breast	38,700	5,400	14
Lymphoma and multiple myeloma	22,300	2,700	12
Lung	125,600	14,000	11
TOTAL	280,000	82,800	30

‡American Cancer Society, Cancer Statistics, 1985.
†Based on Rubin and Carter (1976).
§Melanoma 5,5000; other skin 1,900.
Data from Kapp (31).

32. D.S. Kapp, "Site and disease selection for hyperthermia clinical trials." Int. J. Hyperthermia, 1986; 2:139-156.

In clinical studies, hyperthermia has demonstrated the ability to improve local tumor control and this improve the local failure rates. Laboratory and clinical studies have shown that hyperthermia by itself is tumoricidal and the efficacy is enhanced when hyperthermia is combined with radiation therapy. When using radiation therapy alone for treatment, tumor control often cannot be achieved without using a radiation dose which causes unacceptable damage to surrounding normal tissue, limiting the potential usefulness of radiation. Thus, the goal of the addition of hyperthermia to radiation therapy should be to selectively increase the effectiveness of the maximum tolerable radiation dose. Clinical studies have demonstrated that hyperthermia increases the effect of radiation on tumors and thus increases the efficacy and usefulness of radiation for the treatment of cancer.

The clinical studies reviewed and referenced demonstrate that the use of hyperthermia in conjunction with radiation therapy to treat the following sites and histologies would result in significant patient benefit from improved local/regional control without a significant increase in morbidity: local/regional recurrences and metastases of breast cancer, metastases and recurrences from head and neck cancers, malignant melanoma, recurrent basal or squamous cell carcinomas, colorectal cancer, pelvic recurrences or metastases, cancer of the urinary bladder, prostatic cancer, soft tissue sarcomas, bone tumors, carcinoma of the uterine cervix and uterine corpus, inoperable deep tumors, recurrent metastatic tumors from unknown primary sites, Hodgkin's disease, recurrent or previously untreated malignant brain tumors, and even rarer histopathologic types of cancers such as adenocystic carcinomas and Merkel cell tumors.

Dewhirst, *et. al.*[33] presented an *overview* of the field of hyperthermia to a National Cancer Institute Hyperthermia Workshop. The authors stated that, "No other cancer treatment methodology under development today has direct cytotoxicity along with the potential to enhance tumor specific radiation dose by a factor of 2 with minimal cost in normal tissue toxicity."§

---

33 M, Dewhirst, P. Corry, "Future directions for multi-institutional clinical trials in hyperthermia." A National Cancer Institute Workshop, Washington, DC, 1992.

---

§This article was prepared by Dixie Toolson using selected controlled studies. Please send date, information, and studies for inclusion in future updates to her attention at BSD Medical Corp., 2188 W. 2200 S., SLC, UT 84119.