LOCAL HYPERTHERMIA FOR DEEP TUMORS

HAIM I. BICHER, M.D. AND RALPH S. WOLFSTEIN, M.D.

Consensus on *Hyperthermia for the 1990s*
Edited by H.I. Bicher *et al.*
Plenum Press, New York, 1990

Bicher Cancer Institute, Los Angeles, California, U.S.A.

Hyperthermia for superficial tumors has been considered standard treatment since 1984, based on multiple reports showing synergistic therapeutic advantage in combination with radiotherapy compared to irradiation alone (Table l). Results of external hyperthermia treatments for deep tumors combined with irradiation or chemotherapy have shown significant improvement over controls (24). While side effects of deep treatment have not been greater than with superficial hyperthermia, tolerance of regional deep heating has been poor, with treatment limiting pain and/ or systemic stress in most patients (25, 26). Local deep treatment on the other hand has been well tolerated (27, 28).

Bicher Cancer Institute, Los Angeles, California, U.S.A.

TABLE 1. COMPLETE RESPONSE TO IRRADIATION (RT) ALONE VERSUS (RT) AND HYPERTHERMIA (HT) FOR SUPERFICIAL TUMORS

AUTHOR	EVALUABLE PATIENTS	RT ALONE	RT AND HT
ARCANGELI (1)	163	38%	74%
SCOTT (2)	62	39%	87%
U (3)	14	14%	86%
KIM (4, 5)	238	39%	72%
OVERGAARD (6)	101	39%	62%
CORRY (7)	33	0	62%
HIRAOKA (8)	33	25%	71%
LI (9)	124	29%	54%
SHIDNIA (10)	185	33%	64%
PEREZ (11)	154	41%	69%
VAN DER ZEE (12)	71	5%	27%
STEEVES (13)	90	31%	65%
DUNLOP (14)	86	50%	60%
GOLDOBENKO (15)	65	86%	100%
MURATKHODZHAEV (16)	313	25%	63%
LINDHOLM (17)	85	25%	46%
VALDAGNI (18)	78	36%	73%
EMAMI (19)	116	24%	59%
MARMOR (20)	15	7%	47%
GONZALES (21, 22)	46	33%	50%
SUGIMACHI (23)	129	52%	80%

In this paper results of local deep treatment using parallel opposed microwave applicators are analyzed, including a phase I study of 25 cases previously reported (27).

Bicher Cancer Institute, Los Angeles, California, U.S.A.

MATERIALS AND METHODS

Patients had advanced primary cancer, post treatment recurrence or metastatic disease. Of 121 evaluable treatment 73 had hyperthermia combined with radiotherapy and 48 with chemotherapy. Dosages of irradiation varied widely, depending on normal tissue tolerance and treatment goal. Chemotherapy drug and dosage were appropriate to the case, determined in cooperation with the medical oncologist, with consideration of maximal interaction with Hyperthermia and minimal side effects.

Hyperthermia was delivered by two 300 MHz external applicators, parallel opposed and operated in phase (POPAS)* at power up to 800 watts evenly divided (29). Applicators are standard design 300 MHz 20x23cm horn waveguide with air gap coupling. Prior to clinical studies appropriate in vitro and in-vivo studies were performed. Therapeutic temperatures were obtained centrally in phantoms and pigs up to 20cm thick. A flow of cooled air through an aperture in the applicator enhanced homogeneity of the heat field.

Hyperthermia was given twice a week in early clinical trials, more recently five days per week, over five weeks or throughout the radiotherapy course if longer. Standard radiotherapy fractionation was used, with treatment 5 days per week within 2 hours of hyperthermia, either before or after. One or two fields were treated each day; usually two fields were required to adequately cover large tumors or extensive disease in liver and lung. Each hyperthermia treatment was given for one hour, with the goal of achieving 42 degrees Celsius minimum tumor temperature for 30 minutes. Thermometry throughout each session utilized two triple junction copper-constantan microthermocouples (100 micron)* inserted in tumor when feasible and in normal tissue or on skin surface. Temperature readings were obtained at 4 - 5 minute intervals with power on - off cycle controlled by a computer system that also recorded a permanent temperature record.

Each patient was treated within FDA approved protocol guidelines and signed the appropriate consent form.

RESULTS

At least partial response was obtained in 67% overall, 86% with hyperthermia combined with at least 30 Gy irradiation, 55% with less irradiation, and 62% with chemotherapy. Impact of radiation dose on complete response rates was more dramatic: 46% with more radiation versus 8 – 10% for low dose or no radiation (Table 2). Patient tolerance was excellent. No patient discontinued treatment because of iatrogenic signs of symptoms. Thermal burns occurred in 5% at some time during the treatment course, usually at the first or second hyperthermia session presumably because the patient was not yet fully aware of the danger. Thermometry is not sufficient to avoid burns, and we must rely on the patient to inform us as soon as pain develops. Two patients had pneumothorax, secondary to thermocouple insertion requiring 1 day in hospital. One patient with extensive abdominal disease developed ileus, at first suspected to be bowel obstruction, possible an effect of hyperthermia. Patients generally perspired profusely. Core temperatures did not rise significantly, never more than 2 degrees Celsius and usually much less.

TABLE 2. POPAS RESPONSE BY RADIATION DOSE

RADIATION	#	CR (%)	PR (%)	HR + SD (%)
30Gy (+)	35	16 (46)	14 (40)	5 (14)
20Gy (-)	38	3 (8)	18 (47)	17 (45)
0	48	5 (10)	25 (52)	18 (38)
TOTAL	121	24 (20)	57 (47)	40 (33)

COMPLICATIONS: 6 Skin Burns, 2 Pneumothorax, 1 Ileus

Results were significantly better with a greater number of hyperthermia treatments. CR plus PR was 73% after 25 treatment sessions versus 48% after 10 treatments (Table 3), discussed further elsewhere (30).

TABLE 3. POPAS RESPONSE BY HYPERTHERMIA DOSE

Dose	#	CR (%)	PR (%)	MR + SD (%)
25	92	19 (21)	48 (52)	25 (27)
10	29	5 (17)	9 (31)	15 (52)

Results were equivalent for chest, pelvic and pancreatic tumors, in the 70% CR + PR range, relatively less (47%) for other abdominal lesions (Table 4).

TABLE 4. POPAS RESULTS BY SITE

Site	#	CR	PR	(CR + PR)	SD	NR
Thorax	39	10	19	(74%)	4	6
Pancreas	14	1	9	(71%)	2	2
Other Abd.	36	4	13	(47%)	8	11
Pelvis	32	9	16	(78%)	5	2
TOTAL	121	24	57	(67%)	19	21

Bicher Cancer Institute, Los Angeles, California, U.S.A.

The types of lesions treated in the chest are shown in Table 5. Complete local control was obtained in 3 of 4 patients treated by full dose radiation with curative intent, 2 lung and 1 esophagus. One patient with adenocarcinoma metastatic to mediastinum remains free of disease at two years, while the others died from metastatic disease. Of the 29 patients given 39 courses of hyperthermia treatments for thoracic lesions, 5 of 10 with primary lung cancer lived over one year; as did 6 of 18 others given palliative treatment. Metastatic lung lesions represented the majority of treated thoracic disease (Table 5). Patients usually had bilateral disease progressive despite other previous treatment. Hyperthermia was given over five weeks along with 1500 rad in 15 fractions to the predominantly involved lung. The other lung was then usually treated, depending on response to the initial course. At least 50% tumor regression was achieved in 76% of 21 treatment courses given for lung metastasis.

TABLE 5. THORACIC CANCER, RESPONSE BY CELL TYPE

Type	#	CR	PR	SD	NR
Adenocarcinoma, Lung	7	2	2	2	1
Squamous Cell Ca, Lung	2	_	2	-	-
Oat Cell Ca, Lung	4	4	-	-	-
Squamous Cell Ca Esophagus	1	1	-	-	-
Mesothelioma	2	-	2	-	-
Sarcomas	2	-	-	1	1
Lung Metastasis	21	3	13	1	4
Total	39	10	19	4	6

Except for pancreatic primaries, treated abdominal lesions were metastatic, mostly in liver (Table 6). Of 9 patients given 14 treatment courses for pancreatic adenocarcinoma, all with liver and/or nodal spread, 3 survived 1 - 2 years following the initial treatment course. All but one had at least partial response and profound palliation. The one patient who survived 2 years had 3 treatment courses, 2 with 5 FU infusion and the last with 45 Gy irradiation. CT scan showed complete resolution of the left lobe liver invasion and adenopathy after the first course, and of the primary after thermoradiotherapy. He died of sepsis; no cancer was found at autopsy. The clinical course was striking in this 48 year old man. Pain, extreme weakness and anorexia reversed within two weeks of initiation of thermochemotherapy, completely alleviated at completion of the course; after which he went on a two week hiking trip. He completely regained his 80 pound weight loss and lived a normal life for 18 months. The other 28 patients with other abdominal tumors, mostly liver metastasis, had 36 treatment courses. Response was often of short duration but prolonged by additional treatment, most often by thermochemotherapy. Radiotherapy was given with only 14 of 50 abdominal hyperthermia treatment courses. Interestingly response was much better in metastatic disease treated with chemotherapy, or in a few cases with hyperthermia alone, than radiotherapy (10-20 Gy): 4CR + 1OPR (58%) versus 2PR (25%) respectively.

Bicher Cancer Institute, Los Angeles, California, U.S.A.

TABLE 6. ABDOMINAL CANCER

Type	Patients	Courses
Adenocarcinoma, Pancreas	9	14
Hepatocellular Ca	1	1
Liver Metastasis	20	28
Mesothelioma	1	1
Peritoneal Mets, Ovary	2	2
Lymph Node Mets	4	4

One patient with ovarian cancer developed ascites 8 months after partial regression of pelvic regression of pelvic recurrence, with complete palliation using hyperthermia combined with 2400 rad in 100 rad daily fractions to the pelvis. Treated with hyperthermia alone to two abdominal fields, ascites was completely controlled until her death 13 months later.

As in the chest and abdomen, nearly all pelvic treatments were for palliation after failure of intensive previous treatment. Significant palliation was achieved in 90% of pelvic cases, including most of those patients whose tumors remained stable. Complete response was obtained in 9/32 (28%) (Table 7), all in smaller tumors, less than 5cm; but most lesions were quite bulky, in the 10 - 15 cm range. While lesions that showed CR remained controlled, patients treated palliatively generally died at 4 to 8 months post treatment. One lymphoma patient and one prostate patient remain alive at 18 and 23 months respectively, the latter free of disease.

TABLE 7. RESPONSE BY CELL PELVIC CANCER

Type	#	CR	PR	SD	NR
Rec. Colon	13	3	5	4	1
Rec. Ovarian	6	2	4	_	_
Sarcomas	5	_	4	_	1
Prostate	3	2	1	_	_
Lymphoma	3	2	1	_	_
Melanoma	1	_	1	_	_
Rec. Endomet.	1	_	_	1	_
Total	32	9	16	5	2

DISCUSSION

The treatment of metastatic disease, particularly to lung and liver, represents a major problem in cancer management. Chemotherapy is not effective in most patients. Because of sensitivity of normal tissue, radiotherapy can be given effectively to only small areas of the liver and lung. Hyperthermia has been shown to have no apparent effect on normal tissue and to achieve at least temporary control of metastasis in the majority of cases. Local Hyperthermia can, however have no effect on the overall course of metastatic disease, and the disappointingly short survival despite good local tumor response only confirms this obvious fact.

For post radiation recurrence and chemotherapy failure, hyperthermia remains the sole treatment option. Excellent palliative results have been obtained in treatment of recurrent disease in chest, abdomen and pelvis, as earlier demonstrated for recurrent superficial tumors.

Most locoregional external hyperthermia treatment for deep tumors has been for recurrent or metastatic disease, by other groups as well as ourselves. Untreated advanced primary cancer represented 18% of the patient population in a multi-institutional study reported by Storm et al (31), 29% in a multi-institutional study reported by Petrovich et al (32), and 17% in this report. No authors have analyzed results in these patients separately. In our series all patients with a treatment goal of cure had complete regional control; however this included only 5 patients, 2 free of disease at 20 - 25 months. (Prostate and lung adenocarcinoma) and 3 who died of metastasis (2 oat cell, lung; squamous cell carcinoma, esophagus).

Most deep hyperthermia treatment has been regional, employing either magnetic induction at l3.5% MHz with concentric electrodes (Magnetrode, Henry Medical Electronics, Inc., Los Angeles, CA) or an annular phased array (BSD Medical Corporation, Salt Lake City, UT). Of 756 deep tumors treated with the annular array 6% had CR, 26% PR (31). With the annular array 353 treated tumors showed 10% CR, 17% PR (32). In our series results of local deep hyperthermia treatment were 20% CR and 47% PR.

RF capacitive heating (Thermatron FR - 8, Yamamoto Vinyter Co., Osaka) is being used extensively in Japan for local deep heating. This equipment employs an 8 MHz RF generator feeding two opposed disc electrodes. Experience has been reported by Hiraoka et al (33) in only 40 patients. They now exclude patients with subcutaneous fat over 2 cm, after 4 patients, all with thicker fat layer developed fat necrosis. Otherwise treatment was quite well tolerated. Response was 15% CR, 47% PR. These patients had no previous irradiation and received at least 30 Gy with hyperthermia.

Bicher Cancer Institute, Los Angeles, California, U.S.A.

All authors (31-33) and including our current series found significantly better results when hyperthermia was combined with standard radiotherapy, at least 30 Gy (Table 8). Results using hyperthermia combined with low dose irradiation, up to 30 Gy (31, 32) or 20 Gy in our series were little better than with no irradiation (Table 9). Surprisingly combination with chemotherapy was not shown to improve response rates as compared to hyperthermia alone (Table 9). Specifics of chemotherapy type and administration were not discussed in any of these reports. The most common adjunct chemotherapy we have used is 5 FU by intravenous infusion, 250 mg over 24 hours on each day of hyperthermia. Our results with chemotherapy were equivalent to results with low dose radiation, better than could be anticipated with hyperthermia alone. A recent report comparing results of 5 FU given by infusion to the more common bolus technique (34) found objective tumor response to be respectively 30% and 7% and with far less toxicity using infusion. This marked advantage for infusion may well carry over to improved results in combination with hyperthermia.

Bicher Cancer Institute, Los Angeles, California, U.S.A.

TABLE 8. RESULTS WITH AND WITHOUT STANDARD IRRADIATION

Author	#	Treatment		Results		Total	
		30Gy(+)	NO RT	HT or CR%	HT+RT PR%	CR%	PR%
Storm (31)	960	32%		20	40		
			57%	3	20	9	28
Petrovich (32)	353	39%		21	36		
			26%	2	29	10	39
Bicher	121	29%		40	40		
			40%	10	52	24	57
Hiraoka (32)	40	100%		15	47	15	47

TABLE 9. RESULTS WITH HYPERTHERMIA ALONE, WITH CHEMOTHERAPY AND WITH LOW DOSE RADIATION

Author	HT alone			HT + chemo			HT = low RT		
	(#)	CR	PR	(#)	CR	PR	#	CR	PR
Storm (31)	(142)	3%	20%	(405)	3%	20%	(107)	5%	33%
Petrovich (32)	(47)	2%	34%	(42)	2%	26%	(121)	3%	42%
Bicher				(48)	10%	52%	(38)	8%	47%

Bicher Cancer Institute, Los Angeles, California, U.S.A.

Tumor stabilization (SD) for at least 2 months was achieved in 16% in our series, and for at least 3 months in 15% in the series reported by Storm (3l). Both groups consider this an important criterion (35) separate from progressive disease (NR) both clinically and physiologically. Most patients with SD have either or both significant palliation and improved general condition. Extensive central necrosis is usually noted in stable tumors on CT and pathologic examination of tumors excised following treatment. Lack of tumor regression despite massive cell kill most likely relates to collapse of tumor microvasculature, one of the main mechanisms of thermal effect (36, 37).

Local deep hyperthermia is easily tolerated, far better than regional treatment. A comparison of the annular array with capacitive heating in the same 13 patients with abdominal or pelvic tumors showed no significant difference in tumor temperatures; however duration of treatment using the annular array was limited by increase in body temperature and pulse rate (38). Comparison of the two regional heating devices in the same 23 patients with abdominal or pelvic disease showed treatment limiting factors in 7/14 with pelvic tumors treated by the annular array (AA) and 13/14 using the Magnetrode (CC). The authors concluded that “the AA is superior to the CC for pelvic treatment and that both devices have limitation in abdominal treatment" (25).

A single report in the medical literature compares results of definitive radiotherapy alone or combined with hyperthermia for deep tumors. Hornback et al (24) treated 33 patients with stage III B cervix carcinoma each receiving 25 MeV photon beam irradiation and two Cesium insertions to a total minimum tumor dose of 65 Gy at the lateral pelvic wall. Eighteen of the 33 also received hyperthermia on a daily basis 10 - 15 minutes following each radiation fraction, using a device with two anterior and two posterior 434 MHz microwave antennae. Acute radiation toxicity was the same with or without hyperthermia, "and the addition of heat caused minimal discomfort". Tumor response was subjectively thought to be more rapid in the hyperthermia group. Complete local control without recurrence was achieved in 8/15 (53%) after irradiation alone versus 13/18 (72%) after combination of irradiation and hyperthermia. Median survival in the two groups was 26 and 36 months respectively.

In contemplating these results what can be said as to the appropriate use of hyperthermia for deep tumors? Hyperthermia for deep tumors has been sufficiently evaluated that it is ready now to be considered standard therapy. Hyperthermia offers palliation, hope and improved quality of life when other treatment options have been exhausted. For patients with untreated advanced primary cancer hyperthermia combined with standard radiotherapy offers a significantly better chance for local control. The use of combination treatment should be strongly considered before giving radiotherapy without hyperthermia. Local hyperthermia can be given for tumors in any body region safely and with excellent patient tolerance, with equivalent tumor response rates in thorax, abdomen and pelvis, in the 70% range in our series.

Bicher Cancer Institute, Los Angeles, California, U.S.A.

BIBLIOGRAPHY

1) Arcangeli, G; Benassi, M; Cividalli, A; et al: Radiotherapy and hyperthermia. Analysis of clinical results and identification of prognostic variables. Cancer 60: 950 - 956, 1987.

2) Scott, RS; Johnson, RJR; Story, KV; et al: Local hyperthermia in combination with definitive radiotherapy: Increased tumor clearance, reduced recurrence rate in extended Follow - up. lnt. J. Radiat. Oncol. Biol. Phys. 10: 2119 - 2123, 1984.

3) U, R; Noell, T; Woodward, KT; et al: Microwave - induced local hyperthermia in combination with radiotherapy of human malignant tumors. Cancer 45: 636 - 646, 1980.

4) Kim, JH; Hahn, EW; Antich, PE: Radiofrequency hyperthermia for clinical cancer therapy. Natl. Cancer lnst. Mongr. 61: 339 -342, 1982.

5) Kim, JH; Hahn, E W; Ahmed, SA; et al: Combination hyperthermia and radiation therapy for malignant melanoma. Cancer 50: 478 - 482, 1982.

6) Overgaard, J The current and potential role of hyperthermia in radiotherapy. Int. J. Radiat. Oncol. Biol. Phys. 16: 535 – 549, 1989

7) Corry, Pm; Barlogie, B; Tilchen, EJ; et al: Ultrasound induced hyperthermia for the treatment of human superficial tumors. Int. J. Radiat. Oncol. Biol. Phys. 8: 1225 – 1229, 1982

8) Hiraoka, M; Jo, S; Dodo, Y; et al: Clinical results of radiofrequency hyperthermia combined with radiation in the treatment of radioresistant cancer. Cancer 54: 2898 - 2904, 1984

9) Li, RY; Wang, HP; Lin, SY; et al: Clinical evaluation of combined radiotherapy and thermotherapy on carcinoma of the breast. Clin. Oncol. 12: 73 - 76, 1985

10) Shidnia, H; Hornback, NB; Shupe, RE; et al: Correlation between hyperthermia and large dose per fraction in treatment of Malignant Melanoma (Abstr.) Int. Clin. Hyperthermia Soc. Meeting, Lund Sweden, 1987.

11) Perez, Ca; Kuske, RR; Emani, B et al: Irradiation alone or combined with hyperthermia in the treatment of recurrent carcinoma of the breast in the chest wall. A nonranomized comparison. Int. J. Hyperthermia 2: 179 - 187, 1986

12) Van Der Zee, J; Van Rhoon, GC; Wike - Hooley, JL; et al: Clinically derived dose effect relationship for hyperthermia with low dose radiotherapy. Br. J. Radiol. 58: 243 - 250, 1985

13} Steeves, RA; Severson, SB; Paliwal, BR; et al: Matched - pair analysis of response to local hyperthermia and megavoltage electron therapy for superficial tumors. Endocurietherapy / Hyperthermia Oncol. 2: 163 - 170, 1986

14) Dunlop, PRC; Hand, JW; Dickinson, RJ; et al: An assessment of local hyperthermia in clinical practice. Int. J. Hyperthermia 2: 39 - 50, 1986.

15) Goldobenko, GV; Durnov, LA; Knysh, VI; et al: Experience in the use of thermoradiotherapy of malignant tumors. Med. Radiol. 32: 36 - 37, 1987.

16} Muratkhodzhaev, NK; Svetitsky, PV; Kochegarov, AA; et al: Hyperthermia in therapy of cancer patients. Med. Radiol. 32: 30 - 36, 1987.

17) Lindholm, CE; Kjellen, E; Nilsson, P; et al: Microwave - induced hyperthermia and radiotherapy in human superficial tumors. Clinical results with a comparative study of combined treatment versus radiotherapy alone. Int. J. Hyperthermia. 3: 393 - 411, 1987.

18) Valdagni, R; Amichetti, M; Pani, G: Radical radiation alone versus radical radiation plus microwave hyperthermia for N3 neck nodes: A prospective randomized clinical trial. Int. J. Radiat. Oncol. Biol. Phys. 15: 13 - 24, 1988

19) Enami, B; Perez, CA; Konefal, J; et al: Thermoradiotherapy of malignant melanoma. Int. J. Hyperthermia 4: 373 – 381, 1988

20) Marmor, JB; Hahn, GM; Combined radiation and hyperthermia in superficial human tumors. Cancer 46: 1986 - 1991, 1980.

21) Gonzalez, D; Van Dijk, JDP; Blank, LECM; et al: Combined treatment with radiation and hyperthermia in metastatic malignant melanoma. Radiother. Oncol. 6: 105 - 113, 1986

22) Gonzalez Gonzalez, D; Van Dijk, JDP; Blank, LECM; et al: Chest wall recurrence of breast cancer: Results of combined treatment with radiation and hyperthermia. Radiother. Oncol. 12:95 - 103: 1988

23) Silberman, AW; Rand, RW; Krag, DN; et al: Effect of localized magnetic - induction hyperthermia on the brain. Cancer 57: 1401 - 1404, 1986

24) Hornback, NB; Shupe, RE; Shidnia, H; et al: Advanced stage III B cancer of the cervix treatment by hyperthermia and radiation. Gyn. Oncol. 23; 160 - 167, 1986.

25) Sapozink, MD; Gibbs, FA; Thomson, JW; et al: A comparison of deep regional hyperthermia from an annular array and a concentric coil in the same patients. Int. J. Radiat. Oncol. Biol. Phys. 11: 179 - 190, 1985

26) Pilepich, MV; Myerson, RS; Emami, BN; et al: Regional hyperthermia assessment of tolerance to treatment. Int. J. Radiat. Oncol. Biol. Phys. 14: 347 - 352, 1988

27) Bicher, HI; Wolfstein, RS: Local hyperthermia for deep tumors – Experience with three techniques. J. Microwave Power 21: 21st International Microwave Power Symposium Summaries, 103 – 104, 1986

28) Hiraoka, M; Jo, S; Akuta, K; et al: Regional hyperthermia for cancer. Am. J. Surgery 143: 586 - 590, 1982

29) Bicher, HI; Moore, DW; Wolfstein RS: Air – cooled 300 MHz applicators used in a parallel opposed phased system (POPAS). (Abstr.) Int. J. Radiat. Oncol. Biol. Phys. 11: S1: 217, 1985

Bicher Cancer Institute, Los Angeles, California, U.S.A.

30) Bicher, HI; Wo1fstein, RS: Local superficial and deep hyperthermia - Factors affecting -tumor response and patient survival (Abstr). Presented at 37th Annual Meeting of the Radiation Research Society, Seattle, Wash. 3/18 - 23/ 1989

31) Storm, K; Baker, HW; Scanlon, EF; et al: Magnetic induction hyperthermia. Results of a 5 year multi-institutional national cooperative trial in advanced cancer patients. Cancer 55: 2677 - 2687, 1985

32) Petrovich, Z; Langholz, B; Gibbs, FA; et al: Regional hyperthermia for advanced tumors: A clinical study of 353 patients. Int. J. Radiat. Oncol. Biol. Phys. 16: 601 - 607, 1989

33) Hiraoka, M; Jo, S; Akuta, K; et al: Radiofrequency capacitive hyperthermia for deep-seated tumors. II. Effects of thermoradiotherapy. Cancer 60: 128 - 135, 1987

34) Lokich, JJ; Ahlgren, JD; Gullo, JJ; et al: A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: A Mid - Atlantic Oncology Program study. J. Clin. Oncol. 7: 425 - 432, 1989

35) Storm, KF; Scanlon, EF; Baker, HW; et al: Tumor stabilization after hyperthermia: An important criterion of response to thermal therapy. J. Surg. Oncol. 34: 143 – 149, 1987

36) Bicher, HI.; Hetzel, FW; Sandhu, TS; et al: Effects of hyperthermia on normal and tumor microenvironment. Radiology 137: 523 - 530, 1980

37) Bicher, HI; Hetzel, FW; Sandhu TS: Physiology and morphology of tumor microcirculation in hyperthermia. In Storm, FK (ed): Hyperthermia in Cancer Therapy. Year Book Medical Publishers, 1985, pp 207 - 222.

38) Egana, S; Tsukiyana, I; Akine, Y; et al: Hyperthermia therapy of deep seated tumors: Comparison of the heating efficiencies of an annular array applicator and a capacitively coupled radiofrequency system. Int. J. Radiat. Oncol. Biol. Phys. 14, 521 - 528, 1988.