Effect of Microwave Hyperthermia on Radiotherapy of Human Malignant Tumors

—An Analysis of Clinical Response of 42 Patients—

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Radiobiological and clinical evidences indicate that hyperthermia combined with ionizing radiation produces a significant improvement in therapeutic effect of cancer.

In general, malignant cells are more sensitive to heat than normal cells in the heat range of 41~45℃.

We report the experiences obtained from 42 patients with advanced malignant neoplasms managed with 2,450 MHz microwave-induced local hyperthermia and ionizing radiation at the Department of Radiology, Kangnam St. Mary's Hospital, Catholic University Medical College. A clinical analysis of 42 thermoirradiated patients showed result of 11(26%), 15(36%), 11(26%) and 5(12%) patients with complete response (CR), partial response (PR), minor response (MR) and no response (NR), respectively. Histologically, there were 17(40.2%) squamous cell carcinomas, 12(28.6%) adenocarcinomas and 6(14.3%) miscellaneous cancers. Eleven patients with CR consisted of five squamous cell carcinomas, five adenocarcinomas, and one chloroma. Among 15 patients with PR were five squamous cell carcinomas, five adenocarcinomas, three unknown primary tumors, and one poorly differentiated, and miscellaneous tumor each.

Key Words: Microwave, Hyperthermia, Radiotherapy, Malignant tumor, Clinical response.

INTRODUCTION

Based on the results of experimental studies on the thermal distribution in an agar phantom and transplantable animal tumor,[1,2] we have practiced local hyperthermia using a 2,450 MHz microwave as an adjuvant to cancer treatment in 42 patients with various superficially located malignancy at the Division of Therepeutic Radiology, Department of Radiology, Catholic University Medical College since March 1985.

The treatment plans of 42 cancer patients were hyperthermia with radiation therapy and/or chemotherapy.

We analyzed the clinical response of each treatment scheme according to the primary tumor sites, histologic diagnosis, radiation dose and number of heating, and complications in the course of the trials.

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METHODS AND PATIENTS

Local hypethermia was tried by 2,450 MHz microwave in 42 cancer patients having superficial lesions.[3,4] Radiation was given using a 6 MV linear accelerator up to a total dose, which varied according to the patients and diagnosis and with generally accepted fractionated radiation protocols. Heat was delivered by means of 2,450 MHz microwave generator using contact applicator.[1] The temperature was not measured in all patients but some feasible ones. The temperature was monitored at a regular inteval, with the power off for a couple of seconds, by inserting a thermocouple wire inside the plastic sheath of a 22 gauze Angiocath® placed previously into the lesion.[1]

Heat at 42~44℃ for 30 minutes a day was applied every 72 hours, twice a week, immediately after daily fractionated irradiation, for a total of 10~12 hypertheric sessions.[3,5~7]

The tumor response was estimated by following

criteria. The measurable superficial lesion at the time of the maximum response were complete response (CR, complete disappearance), partial response (PR, 50% or more reduction in size of the lesion), minor response (MR, less than 50% reduction in size of the lesion) and no response (NR) at the end of treatment or soon afterward.[2~5,7~9]

The complications in the course of treatment were expressed as absent or present.[6]

Table 1. Age and Sex Distribution

Age \ Sex	Male	Female	Total (%)
0 – 19	0	0	0 (0)
20 – 39	2	4	6 (14.2)
40 – 59	12	12	24 (57.1)
60 – 79	8	3	11 (26.2)
80 –	1	0	1 (2.5)
Total	23 (54.8)	19 (45.2)	42 (100)

RESULTS

1. There were 23 men and 19 women. Twenty-four of 42(57.1%) patients were in the range of 40 to 59 years of age. The median age was 56 (Table 1).

Table 2. Number of Patients Treated by Sites & Primary Tumors

Site / Primary tumor	Head & neck (supraclavicular node)	Chest wall (breast)	Abdomen (perineum)	Extremity (inguinal & axilla)	Total (%)
Head & neck	7				7 (16.7)
Lung	3				3 (7.1)
Breast	5	6			11 (26.2)
Liver	1				1 (2.4)
Uterine cervix			1		1 (2.4)
Anorectum			4		4 (9.5)
Hematopoietic (CML)				1	1 (2.4)
Others *			1	5	6 (14.3)
Unknown primary	7			1	8 (19)
Total (%)	23 (54.8)	6 (14.3)	6 (14.3)	7 (16.6)	42 (100)

* neurofibroma 2, recurrent fibromatosis, chondrosarcoma, synovial sarcoma, metastatic leiomyosarcoma.

Table 3. Clinical Analysis of Hyperthermic Response in 42 Patients

Response / Primary sites	CR	PR	MR	NR	Total (%)
Head & neck	1	2	3	1	7 (17)
Lung		1	1	1	3 (7)
Breast	4	5	2		11 (26)
Liver				1	1 (2)
Uterine cervix				1	1 (2)
Anorectum	1	2		1	4 (10)
Hematopoietic (CML)	1				1 (2)
Others		2	4		6 (14)
Unknown primary		3	1		8 (20)
Total (%)	11 (26)	15 (36)	11 (26)	5 (12)	42 (100)

CR : complete response, disappearance of tumor
PR : partial response, over 50% tumor shrinkage
MR : minor response, less 50% tumor shrinkage
NR : no response, little change of tumor size

2. The primary tumors and treated anatomic sites were listed in Table 2. Treatment of the chest wall or breast proper for breast cancer was 26.2%, metastatic supraclavicular nodes (SCL) of unknown primary 19%, and head and neck 16.7% in decreasing order.

3. The clinical analysis of hyperthermic response to primary tumor was listed in Table 3. Of 42 patients, 11(26%), 15(36%), 11(26%), and 5(12%) showed CR, PR, MR and NR, respectively.

4. The clinical response based on histologic diagnosis was listed in Table 4. Of 42 patients, 17(40.5%), 12(28.6%) and 6(14.5%) were squamous cell carcinomas, adenocarcinomas and miscellaneous cancers, respectively. Eleven CR's were observed in 5 squamous cell carcinomas, 5 adenocarcinomas, and 1 chloroma. Fifteen PR's were observed in 5 squamous cell carcinomas, 5

Table 4. Clinical Response Based on Histology

Histology \ Response	CR	PR	MR	NR	Total (%)
Squamous cell Ca.	5	5	4	3	17 (40.5)
Adenocarcinoma	5	5	2		12 (28.6)
Undiff. large cell Ca.			1		1 (2.4)
Poorly diff. Ca.		1			1 (2.4)
Hepatocellular Ca.				1	1 (2.4)
Leukemia (CML)	1				1 (2.4)
Miscellaneous		1	4	1	6 (14.3)
Unknown primary site		3			3 (7)
Total (%)	11 (26.2)	15 (35.7)	11 (26.2)	5 (11.9)	42 (100)

CR : complete response, disappearance of tumor
PR : partical response, over 50% tumor shrinkage
MR : minor response, less 50% tumor shrinkage
NR : no response, little change of tumor size
Ca. : carcinoma

Table 5. Hyperthermic Response in View of Radiation Dose and Heat Number

Radiation dose (cGy) \ Heat No.	≦4	5–9	10≦	Total (n=42)
0 – < 2,000	1 |	|	|	1 | (1)
2,000≦ – < 4,000	1 |	3 |	|	1 | (4)
		3 |		3 |
4,000≦ – < 6,000	1 |	4 | 3	3 | 1	7 | 5 (22)
		6 |	4 |	10 |
6,000≦	|	| 2	4 | 3	4 | 5 (15)
	1	1 | 1	1 | 2	2 | 4
Total (n=42) CR | MR / PR | NR	3 |	4 | 5	7 | 4	11 | 12
	1	10 | 1	5 | 2	15 | 4
	(4)	(20)	(18)	(42)

Table 6. Comparision of Treatment Results

	CR	PR	MR	NR	Total (%)
(XRT) + H		1	2	3	6 (14.3)
XRT + H	10	10	8	2	30 (71.4)
CX + XRT + H	1	4	1		6 (14.3)
Total (%)	11 (26.2)	15 (35.7)	11 (26.2)	5 (11.9)	42 (100)

XRT : radiation therapy (RT), (XRT) : previous RT, CX : chemotherapy
H : hyperthermia

Table 7. Complications Due to Thermoirradiation

Complication	Number of patients
Erythema	42
Dark pigmentation	5
Moist desquamation	4
Subcutaneous fibrosis	1
Thermal burn	1

adenocarcinomas, 3 unknown primary tumors, and 1 poorly differentiated and miscellaneous tumor each.

5. Table 5 summarized the clinical response in connection with radiation dose and heating number. Ten out of 20 responsive patients (CR+PR) underwent 40~60 Gy/5-7wks irradiation and 5 to 9 sessions of hyperthermia.

6. The composition of each treatment modalities was shown in Table 6. Thirty out of 42 patients (71.6%) were treated with irradiation immediately following hyperthermia.

7. Table 7 summarized the observed complications in the course of this clinical trial. Transient and various degree of erythema was observed in all patients. Pigmentation and moist desquamation were also observed at the thermoirradiated patients. One superficial burn which developed on the keloid scar in the patient with recurrent breast cancer has regressed spontaneously.

DISCUSSION

Radiotherapeutic doses required to sterilize radioresistant tumors are limited by normal tissue tolerance.[3~10] Various techniques have been applied to compensate for this limitation including hyperbaric oxygenation, hyperfractionation and protracted ionizing radiation doses, high linear energy transfer (LET) radiation and chemosensitizer with varying success.[3,7,8]

The effects of hyperthermia in the treatment of cancer are: (1) moderate hyperthermia (41~44℃) produced direct thermal effects and also potentiates ionizing radiation damages by inhibition of repair and recovery of sublethal and potentially lethal damage, (2) cells in synthetic (S) phase are usually radioresistant but sensitive to heat, (3) radioresistant hypoxic cells do not protect cells from damage by heat, (4) cells in low pH environment, as in necrotic tissue, are more sensitive to heat, (5) nutritionally deprived cells are more sensitive to heat than adequately fed cells, (6) selective accumulation of heat in tumor with a poor blood supply than the surrounding normal tissue.[2~10]

Ultrasound, radiofrequency, microwaves and heated perfusion solutions are now available for the induction of local hyperthermia that can be adapted to various clinical needs.[1~11] Ultrasound is easily generated, focused, and localized but air-fluid and bone interphases may limit its application. Radiofrequency heating penetrates much deeper than microwave does. The former produces relative heat accumulation at the subcutaneous fat layer preventing thermal conduction. In addition, microwave radiation provides convenient and readily controllable local heating with relative simplicity.

Several clinical trials demostrated that hyperthermia plus irradiation can produce high tumor response rates than the irradiation alone.[2~9] 2,450 MHz microwave usually achieve potentially therapeutic temperature to only about 2~4 cm depth.[1~4,6,9]

A variety of hyperthermia and fractionation schemes of irradiation have been tried but the optimal one is yet to be established. We have treated with conventional fractionated irradiation (daily 180~200 cGy, 5x/week), immediately following 30 minutes hyperthermia (every 72 hours interval a

week) up to a total of 10~12 sessions.

No tumor has been shown to be especially sensitive than others although relative radioresistant melanom a is substantially affected by the addition of hyperthermia.[3~11] Microwave thermoirradiation responses of the present series were 11 CR's and 15 PR's. In these responsive groups, the most responsive patients were those received 40~60 Gy irradiation and 5 to 9 hyperthermia heatings. Histologically, 11 CR's consisted of 5 squamous cell carcinomas, 5 adenocarcinomas and 1 chloroma. Fifteen PR's consisted of 5 squamous cell carcinomas, 5 adenocarcinomas, 3 unknown primary primary tumors, and poorly differentiated carcinoma and miscellaneous tumor in each one. A moderate dose of irradiation and localized hyperthermia was shown to induce regression in more than 60% of lesions treated.[2,4,6~9] The most serious complication noted in this study was second-degree burn at the keloid formed in a surgical scar.

The histologies and primary sites lend further confusion in evaluating results. The heat effect is probably nonspecific as no particular primary tumor or histology appeared to respond better or worse than others.[6,7,9]

SUMMARY

Localized hyperthermia can significantly enhance irradiation cytotoxicity in superficial human tumors compared to normal tissue. Clinically, we observed reduction of about 10~20 Gy radiation doses to treat the superficial thermoirradiated tumors, and it was concluded that 2,450 MHz local hyperthermia was safe and beneficial to superficial tumors especially in combination with radiation therapy.

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＝국문초록＝

극초단파를 이용한 국소온열 치료 효과

—표재성 종양 42예의 분석—

가톨릭의과대학 방사선과학교실

윤세철 · 오운경 · 길학준 · 정수미
신 경 섭 · 박 용 휘

인간이 각종 질병치료에 있어 열(온열)을 이용한 것은 고대의학의 시작과 그 역사가 함께 비롯된다. 이러한 온열요법은 방사선치료나 일부 항암약제와 병행할때 그 효과가 상승되며 그 단독 사용 만으로도 암세포를 죽일 수 있음이 최근에 와서 밝혀지고 있고 또한 병태생리학적 기전이 규명되고 있다.

한편, 온열치료기계 및 온도측정장치의 개발로 말미암아 암환자 치료에 온열치료의 임상적 응용이 각광을 받고 있다. 가톨릭의대 강남성모병원 방사선치료실에서는 1985년 3월 이후 1년 9개월 동안에 표재성의 전이 또는 원발암환자 42예(남 23예, 여 19예 ; 평균연령 56세)에서 외부방사선치료 또는 항암약물치료와 병행하여 가정용 전자레인지를 개조하여 만든 2,450 MHz 극초단파를 이용한 온열치료를 실시하였다. 이 중 6예에서는 방사선치료 종료후 재발되었기에 온열치료 단독으로 실시하였다.

온열치료후 임상적 반응은 총 42예 중 종괴의 완전관해 부분관해 소관해 및 무관해율이 각각 11예(26%), 15예(36%), 11예(26%) 및 5예(12%)였다. 조직학적 진단은 편평상피암 17예(40.5%), 선세포암 12예(28.6%) 및 기타암종이 6예(14.5%)였다. 완전관해를 보인 11예의 조직학적 진단은 편평상피암 5예, 선세포암 5예, 녹색종이 1예 였으며, 부분관해를 보인 15예는 편평상피암 5예, 선세포암 5예, 불명암 3예 및 미분화세포암과 기타암종이 각각 1예씩 이었다.

방사선치료선량과 온열치료 횟수와의 관계는 40~50 Gy/5~7주의 방사선치료와 1회 30분씩 주 2회, 총 5~9회의 온열치료를 실시하였던 군에서 가장 온열치료효과가 좋았던 것으로 분석되었다.

한편 온열치료의 부작용으로는 일시적 치료부위 발적이 모든 환자에서 관찰되었으며 수술후 켈로이드에 재발되었던 유방암환자 1예에서 자연치유되는 2도 화상을 경험하였다.