Yonsei Medical Journal
Vol. 35, No. 3, 1994

Combined Treatment of Radiotherapy and Hyperthermia for Unresectable Hepatocellular Carcinoma

**Jinsil Seong[1], Hyung Sik Lee[1], Kwang Hyub Han[2]
Chae Yoon Chon[2], Chang Ok Suh[1] and Gwi Eon Kim[1]**

Eighty-four patients with unresectable primary hepatocellular carcinoma due either to locally advanced lesion or to association with liver cirrhosis were treated with combined radiotherapy and hyperthermia from April 1988 to January 1991. Purpose of this study was to assess thermometry, response rate, toxicity, and survival in those patients.

External radiotherapy was given with a total of 30.6 Gy/3.5wks. Hyperthermia was given twice a week with a total of 6 treatment sessions using an 8 MHz radiofrequency capacitive type heating machine. Each hyperthermia session was started within 30 min following radiotherapy and continued for 30~60 min. Thermal data were analysed with maximum, minimum, and average temperatures of the tumors. Thermal mapping was also done. In thermometry results, maximum, minimum, and average temperatures of the tumors were 41.9±1.3℃, 39.9±1.0℃, and 40.8±0.9℃, respectively. The fraction over 40℃ was 73±32% with a wide variation from 15% to 100%. Among 67 assessable patients, 27 patients showed tumor regression of more than 50% of the original tumor volume (40.3% response rate). Symptomatic improvement was observed in 78.6% of the patients. Acute toxicities during the treatment were mostly acceptable local pain (51.2%) and local fat necrosis (13.1%). The actuarial 1-year, 2-year, and 3-year survival rates were 44.8%, 19.7%, and 15.6%, respectively. Median survival was 6 months.

In view of acceptable toxicities and the current rate of survival, further evaluation of combined treatment of radiotherapy and hyperthermia for unresectable hepatocellular carcinoma is warranted.

Key Words: Radiotherapy, hyperthermia, hepatocellular carcinoma

Primary hepatocellular carcinoma (HCC) is a major malignant disease in parts of Africa and the Orient including Korea (Kew and Gedds, 1982; Kim *et al.* 1984; Li and Shiang, 1980). Surgical resection, while providing the best hope of the cure, is severely limited by the extent of the disease and the high incidence of concurrent hepatic parenchymal disease such as liver cirrhosis (Mori, 1967). Although various therapeutic efforts have been recently made for the treatment of unresectable HCC, its prognosis is still dismal. Radiotherapy (RT) has been of only modest benefit in the treatment of HCC. This is chiefly because the tolerance dose to the whole liver for radiation is generally accepted to be approximately 3500 cGy (Ingold *et al.* 1965; Wharton *et al.* 1973). Due to this restriction on the dose of radiation that can

Received March 15, 1994
Accepted July 20, 1994

[1]Department of Radiation Oncology and [2]Department of Internal Medicine, Yonsei University College of Medicine, C.P.O. Box 8044, Seoul, Korea

Presented at International Congress of Radiation Oncology, Kyoto, Japan, 22 June 1993.

Address request for reprints to: Jinsil Seong, M.D., Ph. D., Department of Radiation Oncology, Yonsei University College of Medicine, C.P.O. Box 8044, Seoul 120-752, Korea

be safely administered, there has been little enthusiasm for radiation as a sole modality in the treatment of HCC.

Therapeutic efficacy of hyperthermia (HT) as an adjuvant to RT has been well defined through numerous clinical trials over the past decade (Abe *et al.* 1986; Lee *et al.* 1989; Loh *et al.* 1988, 1989; Song *et al.* 1986). The rationale of combined treatment of RT and HT is that heat interacts synergistically with ionizing radiation (Bichel *et al.* 1979; Dewey *et al.* 1977). The experiences at the University of Minnesota (Lee *et al.* 1989), Yonsei University (Loh *et al.* 1988), and Japanese multi-institutional study (Abe *et al.* 1986) indicate that capacitive type heating with radiofrequency (RF) is useful in treating deep-seated human tumors. However, its effect in HCC has not been fully documented.

We report here the results of combined treatment of RT and HT for locally advanced HCC with an analysis of the thermal data, toxicity, tumor response, and survival.

Table 1. Characteristics of patients (April 1988-January 1991, 84 pts)

		No. of Patients (%)
Sex:	male	71(84.5)
	female	13(15.5)
Age:	<50	28(33.3)
	≧50	56(66.7)
Performance:	ECOG 0~1	74(88.1)
	ECOG 2	10(11.9)
Liver cirrhosis:	−	31(36.9)
	+	53(63.1)
Liver function status: (Child's class)	A	51(60.7)
	B	28(33.3)
	C	5(6.0)
Tumor size: (mean diameter)	5~10 cm	30(35.7)
	>10 cm	54(64.3)
Tumor type:	single massive	40(47.6)
	multinodular	27(32.1)
	diffuse infiltrative	17(20.3)
AFP(IU/ml):	<400	40(47.6)
	≧400	44(52.4)

MATERIALS AND METHODS

From April 1988 until January 1991, 84 patients with unresectable HCC due to advanced lesion and/or associated cirrhosis, were entered into the present study. Patients were considered eligible for the entry provided the following criteria were met: Diagnosis of HCC established by needle aspiration biopsy or elevated alpha fetoprotein (AFP) more than 400 IU/ml with CT scan finding compatible with HCC, locally advanced, unresectable tumor without evidence of distant metastasis, performance status of ECOG scale 0~2, and absence of either cardiac pacemaker or metal prosthesis.

As shown in Table 1, liver cirrhosis was associated in 63% of the patients. Liver function was good in 60% of the patients according to Child's classification*. The mean diameter of the tumors was more than 5 cm in all patients and it was more than 10 cm in 64% of the patients. In cases of multiple lesions, the mean diameters of each lesion were added. Tumor types were classified according to the radiologic finding; single massive, multinodular, and diffuse infiltrative types were found in 40, 27, and 17 patients respectively.

Radiotherpy was given 1.8 Gy per day, five times a week using 10 MV or 4 MV linear accelerator with a total tumor dose of 30.6 Gy in 3.5 weeks. RT fields included tumors with a generous margin (1.5~2 cm) and the mean field size was 220 cm^2. Whole liver irradiation was always avoided. Mostly parallel opposing portals were used and three portal combination or oblique fields (right anterior oblique & left posterior oblique) were used in some occasions. Hyperthermia using the RF capacitive heating machine, Thermotron RF-8**, was given twice a week with each session 3 days apart for a total of 6 sessions. Each HT session was started within 30 minutes following

*Child's A: bilirubin <2 mg/dL, albumin >3.5 g/dL, no ascites, Child's B: bilirubin 2~3 mg/dL, albumin 3~3.5 g/dL, easily controlled ascites, minimal neurologic symptom, Child's C: bilirubin >3 mg/dL, albumin <3 g/dL, uncontrolled ascites, obvious neurologic symptom.

**Yamamoto Vinyter Co., Japan

RT. When the thermometry was possible, each HT was planned to maintain the temperature of more than 40℃ for 30 minutes. In such cases the power of the machine was shown to be in between 600 watt and 800 watt. The same power was applied to the patients in whom the thermometry was not possible. To prevent overheating of the skin surface, the temperature of the saline bolus between the electrodes and the skin was maintained at 5~10℃.

For the temperature measurement, a 10 cm-long, 19 G angiocatheter was inserted into the tumor mass as deep as possible under the ultrasound guide and a thermocouple*** was placed within the needle lumen. At least 3 points of intratumoral temperatures were measured. From 20 minutes after the start of heating, maximum (Tmax), minimum (Tmin), and average (Tave) temperatures of the tumor were continuously measured and defined as thermal parameters during the steady state. At the end of the treatment, thermal mapping was attempted by pulling the thermocouple 1 cm by 1 cm through the thermometry tract. The fraction of thermal mapping temperatures over 40℃ [F(40℃)] was measured in this way. Thermometry was attempted for all patients but was not performed in 50 patients due to patients' refusal (32 patients) or bleeding tendency (18 patients). In another 18 patients thermometry failed even after the insertion of the angiocatheter due to obstruction of the catheter lumen with blood clots (9 patients), misplacement of the angiocatheter (4 patients), severe pain (3 patients), or profuse bleeding from the needle puncture site (2 patients). So thermometry was successful in 16 patients.

Complete blood count (CBC) and liver function test (LFT) were monitored weekly during the treatment period (about 4 weeks) and monthly after the treatment.

Tumor response was evaluated by the change in tumor size measured in CT scan 1 ~3 months after the treatment: complete disappearance of the tumor was considered as a complete response (CR), decrease of more than 50% of the tumor volume as a partial response (PR), decrease less than 50% of tumor or progression as no response (NR).

All patients were followed until the time of reporting: the minimum follow up period was 10 months and the median follow-up time was 3.5 years. Survival was calculated from the first day of the treatment.

RESULT

Thermal distribution of the tumors

As shown in Table 2, thermal data from 16 patients were analysed. Tmax showed a variation with a mean of 41.9℃ and Tmin also varied with a mean of 39.9℃. In each tumor the differences of Tmax and Tmin were between 0.8℃ and 4.4℃. Mean Tave was 40.8℃ in the range of 39.2℃ and 42.5℃. F(40℃) data in thermal mapping showed a wide variation of the temperatures; it was 100% in 9 among 16 patients whereas it fluctuated from 15% to 65 % in the rest of the patients.

Tumor response (Table 3)

Among 67 assessable patients for tumor

Table 2. Thermal distribution of tumors in 16 patients

Case No.	Tmax(℃)	Tmin(℃)	Tave(℃)	F(40℃)(%)
1	42.8	39.9	41.7	100
2	40.0	38.4	39.8	27
3	43.1	38.7	40.3	40
4	43.2	40.0	41.2	100
5	44.3	41.7	42.5	100
6	42.6	39.0	40.8	100
7	41.3	40.5	41.0	100
8	43.0	41.8	41.9	100
9	41.9	40.5	41.7	100
10	42.4	41.2	41.9	100
11	40.6	38.9	39.2	39
12	39.9	39.2	39.5	15
13	41.7	39.8	41.0	50
14	42.2	40.5	41.6	100
15	40.4	39.5	39.7	65
16	40.6	39.5	39.8	37
Mean±SD	41.9±1.3	39.9±1.0	40.8±0.9	73±32

***Sensortek Inc., Type IT-18, New Jersey

response, 27 patients showed PR response (response rate 40.3%). In one patient, whose tumor had been considered unresectable due to the advanced lesion, a surgical resection was performed following tumor regression. The surgical specimen showed a cluster of necrotic masses surrounded by a thick fibrous capsule. Upon thorough histological examination, massive necrotic areas and marked fibrosis were noted, however, no tumor cell was found (Fig. 1 A-C). Symptomatic improvement

Table 3. Response rate

Response		No. of patients(%)
Objective:	No. of assessable pts.	67(100)
	CR	2(3.0)
	PR	25(37.3)
	NR	40(59.7)
Subjective:	No. of symptomatic pts.	70(100)
	improvement	55(78.6)
	no change	11(15.7)
	aggravation	4(5.7)

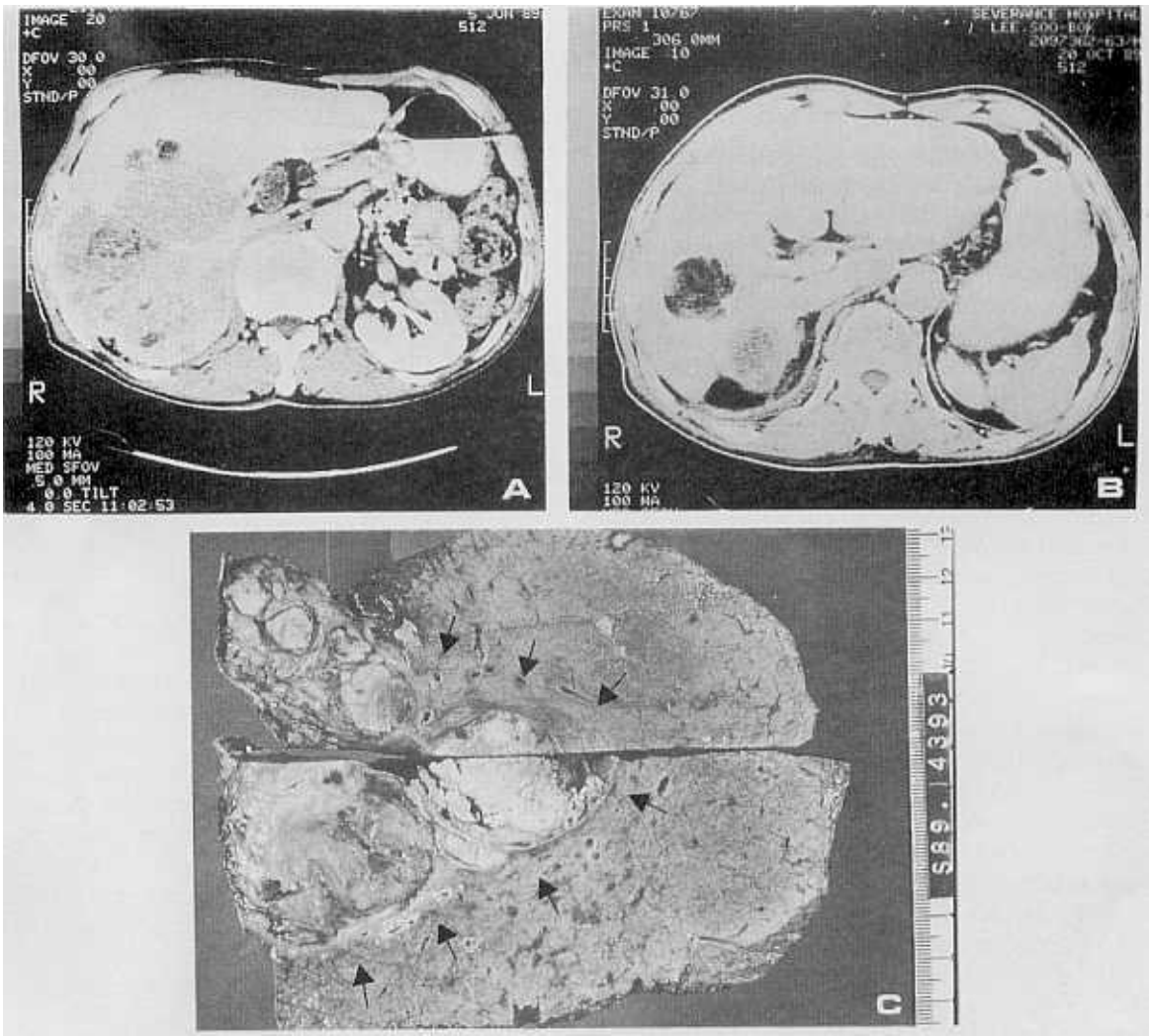

Fig. 1. A case of complete tumor necrosis:
A. Pretreatment CT scan shows a multinodular tumor in the right lobe of the liver
B. Previously shown tumor is remarkably shrunk 3 months after the treatment
C. The resected specimen shows a cluster of necrotic masses surrounded by a thick fibrous capsule (arrows)

Table 4. Toxicites

	No. of patients(%)
Local pain during hyperthermia	43(51.2)
Local fat necrosis	11(13.1)
Nausea and vomiting	7(8.3)
1° burn	7(8.3)
Gastric ulcer	4(4.7)
Hematoma*	4(4.7)

*at the needle insertion site for thermometry

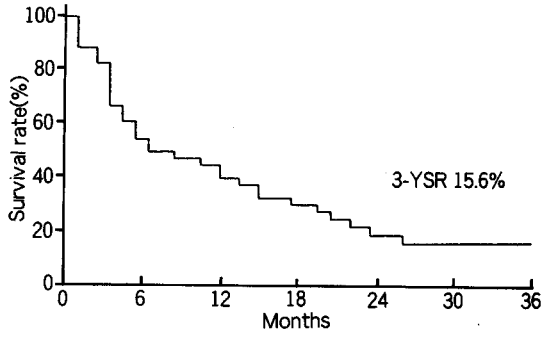

Fig. 2. *Survival curve of 84 hepatocellular carcinoma patients following combined treatment of radiotherapy and hyperthermia*

was observed in 78.6% of the patients who had pain or loss of a sense of well-being.

Toxicities (Table 4)

Fifty-one percent of the patients experienced local pain during hyperthermia, particularly over the skin along the edge of the electrodes. It disappeared immediately after the heating finished and only eleven patients developed subcutaneous fat necrosis over the same area. However, they recovered within one or two months without any treatment. Nausea and vomiting and first degree burn were also noted. Four patients developed gastric ulcers, which required symptomatic medication. Among the patients in whom thermometry was performed, four developed hematoma at the needle insertion site.

CBC did not show any significant change. In serial LFT, mean serum albumin level was constant. One month after the treatment, mean serum alkaline phosphatase level showed a 30% increase of its pretreatment level and mean serum transaminase level also doubled their pretreatment level. Those changes recovered in 3 months after the treatment. Total serum bilirubin level showed slight increase at the end of the treatment and remained constant thereafter.

Four patients died of hepatic failure in the early period of this study. Their common features were: presence of liver cirrhosis with Child's class C, huge tumor size with mean diameter (cm) of 12, 12, 18, and 14, respectively. Either rapid progression of the neoplasm or deterioration of hepatic function due to the treatment might be responsible for their deaths.

Survival

With a median follow-up of 3.5 years, the actuarial 1-year, 2-year, and 3-year survival were 44.8%, 19.7%, and 15.6%, respectively. The survival rate continuously decreased up to 2 years and remained almost constant thereafter. The median survival was 6 months (Fig. 2).

DISCUSSION

There have been several reports on hyperthermic treatment for the liver tumors. Regional RF hyperthermia was combined with cytotoxic chemotherapy for the metastatic hepatic tumors from colorectal carcinomas by Moffat *et al.* (1985). Malignant liver tumors including primary and metastatic carcinomas were treated with thermotherapy combined with chemotherapy, radiotherapy, or embolization in Kyoto University (Nagata *et al.* 1990). However, their experience with HCC is very limited to show any effect of combined treatment of RT and HT and the thermal data was reported only recently.

In this study, the tumors could be heated up to 41.9℃ in mean Tmax and 39.9℃ in mean Tmin. These are in good agreement with Nagata *et al.* (1990) who reported mean

Tmax as 41.2℃ and mean Tmin as 40℃ in thermotherapy of the liver tumors using the same type of heating machine as used in this study. Their study also showed that the normal liver temperature rose to 41.5℃ with a mean of 39.8℃ suggesting only a minimal difference from Tmin of the tumor. In this study, we frequently found that temperature distribution was not uniform at the various point of the tumor or from one treatment to another. Therefore, uniform heating still remains a challenging area of research in hepatomas as well as in other deep-seated tumors.

An attempt to correlate tumor minimum temperature with local response of the tumor was made by Nagata *et al.* (1990). They reported that the tumors heated below 40℃ had the worst response. However, their suggestion needs further investigation because the analysis included all thermal data regardless of histology (HCC, cholangiocarcinoma, and metastatic tumor) or type of combined treatment (radiotherapy, chemotherapy, and embolization). In this study, we couldn't correlate tumor temperture with tumor response due to the limited thermal data of 16 patients. More accumulation of thermal data is required to prove any correlation between the tumor temperature and clinical outcome.

In HCC, thermometry frequently appears to be a risky procedure. In our study, thermometry was successful only in 16 patients (19%) mostly due to patients' refusal and bleeding-related complications. Moreover it couldn't be performed at every session of the hyperthermia. Moffat *et al.* (1985) advocated that the routine use of invasive thermometry seems to be unjustifiable given the questionable quality of the information obtained and the complications. However, it should be noted that overheating of the normal liver can cause serious morbidity and mortality and underheating might have no benefit. Thermometry with acceptable complication can be justified in parallel with many efforts to develop non-invasive thermometry.

The radiation dose in this study was not enough to induce tumor response with radiation alone. El-Domeiri *et al.* (1971) treated 31 patients with radiation doses of 10 to 36 Gy; 70% died within 6 months. Philips and Murikami (1960) showed that radiation doses of less than 20 Gy were ineffective. In this study, we could achieve a tumor response (CR +PR) of 40% with 30.6 Gy and hyperthermia. As shown in the thermal data, tumor temperatures were not high enough to induce cytotoxicity by heat itself. Radiosensitization by heat might have an effect on tumor response. Considering that this study included advanced lesions, which were more than 10 cm in mean diameter of the tumor in 64% of the patients, combined treatment of RT with HT appears to be effective in induction of the tumor response. In Nagata *et al.'s* report (1990), 6 out of 7 HCC patients (85%) showed PR response with RT and HT. However, the number was too small to show any result. In an assessment of tumor response to combination of RT and chemotherapy for HCC, Stillwagon *et al.* (1989) defined PR as a 30% reduction in volume and they achieved 22% PR with a high rate of complication. If we use their definition of PR, our PR rate will approach 60%.

One patient, who showed radiological PR and subsequently underwent surgical resection, proved to be pathologically CR. He is still alive 4 years and 6 months after the treatment. Regression of the tumor can offer a chance for surgical resection in a subset of the patients group. Therefore, combined treatment of RT and HT might be considered as a modality to convert unresectable tumors to resectable ones. Symptomatic improvement was observed in 78.6% of the patients who had pain or loss of a sense of well-being. In consideration of the patient's initial status, the quality of life remained high. This is considered another role of this combined treatment.

Acute toxicities were all self-limiting without a specific treatment. Local fat necrosis developed in 11 patients, whose subcutaneous fat thickness was less than 2 cm. It was thought to be due to the generation of excessive heat near the electrodes. This edge effect can be minimized by uniform application of electrically-conductive jelly over the contact surface for the initial step. Gastric ulcers developed in 4 patients; They improved with oral medication.

Although changes in either CBC or LFT were not remarkable, combined treatment of RT and HT seems to affect liver function significantly in some patients. The common features of the 4 hepatic failure patients were the large size tumor (over 10 cm in mean diameter) and poor liver function before RT and HT (Child's C). It can be thought that even the slightest decrease in the liver function by RT and HT can be dangerous in the marginally functioning liver. A large tumor with poor liver function (Child's C) is not thought to be a good candidate for this combined treatment. Now we limit patient eligibility to Child's A and B by liver function status.

Median survival of unresectable HCC has been reported to be about 4 months by others (16). In this study, median survival was 6 months and 15.6% of the patients survived more than 3 years. Further study to find a subset of the patients who will benefit from this treatment will be continued. To improve survival, the potential role of combined RT and HT as a part of multimodality approach should be further investigated. Dose escalation of radiation should also be investigated for the patients whose tumors are confined to the peripheral site of the liver.

These results imply that this type of combined treatment can be a new opportunity in the management of HCC. In view of acceptable toxicities and current survival results, further evaluation of combined treatment of RT and HT for locally advanced HCC is warranted.

REFERENCES

Abe M, Hiraoka M, Takahashi M, Egawa S, Matsuda C, Onoyama Y, Morita K, Kakehi M, Sugahara T: Multi-institutional studies on hyperthermia using an 8-MHz radiofrequency capacitive heating device (Thermotron RF-8) in combination with radiation for cancer therapy. *Cancer 58: 1589-1595, 1986*

Bichel P, Overgaard J, Nielson OS: Synergistic cell cycle kinetic effect of low doses of hyperthermia and radiation on tumor cells. *Eur J Cancer 15: 1191-1196, 1979*

Dewey WC, Hopewood LE, Saparato SA, Gerweck LE: Cellular response to combination of hyperthermia and radiation. *Radiology 123: 463-470, 1977*

El-Domeiri AA, Huvos AG, Goldsmith HS, Foote FWJr: Primary malignant tumors of the liver. *Cancer 27: 714-719, 1971*

Ingold JA, Reed, GB, Kaplan HS, Bagshaw MA: Radiation hepatitis. *Am J Roentgenol. 93: 200-208, 1965*

Kew MC, Gedds EW: Hepatocellular carcinoma in rural southern African blacks. *Medicine 61: 98-108, 1982*

Kim IS, Kim HJ, Oh HC: The cancer registry program in Kangwha country the first report (July 1982- Jun 1984). *Korean J Epidemiol 6: 100-105, 1984*

Lee CKK, Song CW, Rhee JG, Levitt HS: *Chinical experience with Thermotron RF-8 capacitive heating for bulky tumors: University of Minne sota experience.* In: Steeves, R.A., eds. *The Radiologic Clinics of North America. Philadelphia:* W.B. Saunders Company; *1989, 543-558*

Li FP and Shiang EL: Cancer mortality in China. *J Natl Cancer Inst 65: 217-221, 1980*

Loh JJK, Seong JS, Suh CO, Roh JK, Kim BS, Kim GE: Hyperthermia using 8 MHz capacitive type in the treatment of cancer. *J Korean Med Assoc 31: 1229-1239, 1988*

Loh JJK, Seong JS, Suh CO, Kim GE, Chu SS, Pak KR, Lee CG, Kim BS, Kim SG, Seel DJ: Cooperative clinical studies of hyperthermia using a capacitive type heating device. *Yonsei Med J 30: 72-80, 1989*

Moffat FL, Gilas T, Calhoun K, Falk M, Dalfen R, Rotstein LE, Makowka L: Further experience with regional radiofrequency hyperthermia and cytotoxic chemotherapy for unresectable hepatic neoplasia. *Cancer 55: 1291-1295, 1985*

Mori W: Cirrhosis and primary cancer of the liver: Comparative study in Tokyo and Cincinnati. *Cancer 20: 627-631, 1967*

Nagata Y, Hiraoka M, Akuta K, Abe M, Takahashi M, Jo S, Nishimura Y, Masunaga S, Fukuda M, Imura H: Radiofrequency thermotherapy for malignant liver tumors. *Cancer 65: 1730-1736, 1990*

Okuda K, Obtsuki J, Obata H: Natural history of hepatocellular carcinoma and prognosis in relation to treatment. *Cancer 56: 918-928, 1985*

Philips R, Murikami K: Primary neoplasms of the liver: Results of radiation therapy. *Cancer 13: 714-719, 1960*

Song CW, Rhee JG, Lee CKK, Levitt SH: Capacitive heating of phantom and human tumors with an 8 MHz radiofrequency applicator (Thermotron RF-8). *Int J Radiat Oncol Biol Phys 12: 365-372, 1986*

Stillwagon GB, Order SE, Guse CG, Klein JL, Leichner PK, Leibel SA, Fishman EK: 194 hepatocellular cancers treated by radiation and chemotherapy combinations: toxicity and response: a Radiation Therapy Oncology Group Study. *Int J Radiat Oncol Biol Phys 17: 1223-1229, 1989*

Wharton JT, Delclos L, Gallager S: Radiation hepatitis induced by abdominal irradiation with the cobalt 60 moving strip technique. *Am J Roentgenol 117: 73-81, 1973*