Cancer Chemother Pharmacol (1992) 31 (Suppl I): S119–S127

Cancer Chemotherapy and Pharmacology

Phase II trial for combined external radiotherapy and hyperthermia for unresectable hepatoma*

Byung Soo Kim[1], Hyun Cheol Chung[1], Jin Sil Seong[2], Chang Ok Suh[2], and Gwi Eon Kim[2]

[1] Division of Cancer Chemotherapy, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea
[2] Division of Radiotherapy, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea

Summary. Hepatocellular carcinoma is a major malignant disease in parts of Africa and Asia, including Korea. Surgical resection, which represents the best hope for cure, is limited by the extent of the disease and the high incidence of concurrent liver cirrhosis in Korea. We designed a phase II trial of combined external radiotherapy and hyperthermia for hepatocellular carcinoma that was unresectable due to either locally advanced lesions or associated liver cirrhosis so as to evaluate the efficacy and the safety of this combination regimen. This trial was performed at Yonsei Cancer Center between April 1988 and July 1988. External radiotherapy was delivered to a total dose of 3060 cGy/3.5 weeks. Hyperthermia was applied twice a week for a total of six treatment sessions using an 8-MHz radiofrequency capacitive-type heating device, i. e., Thermotron RF-8 and Cancermia. In all cases, hyperthermia was carried out within 30 min of the radiotherapy for a period of 30–60 min. The temperature in the tumor was measured by inserting a thermocouple into the tumor mass under ultrasonographic guidance in patients who did not have a bleeding tendency. The tumor response was assessed by CT scan after completion of the designed treatment. No complete response was obtained. However, a symptomatic improvement in abdominal pain was observed in 78.6% of cases and a partial response was achieved in 40% of the patients. The most important factor affecting the tumor response was the type of tumor (single massive, 71.4%; diffuse infiltrative, 20%; multinodular, 0; $P < 0.005$). The 1-year survival values determined for all patients and for the partial responders were 34% and 50%, respectively. The overall median duration of survival was 6.5 months. The median duration of survival for the partial responders was longer than that for the nonresponders (11 vs 5 months; $P < 0.05$). A mild degree of heat sensation, fever, first-degree burns of the skin, and nausea were observed as treatment-related adverse reactions. In conclusion, although this study is being continued, the results obtained thus for indicate that combined radiotherapy and hyperthermia seem to be effective in providing local tumor control and pain palliation in unresectable hepatocellular carcinoma while producing an acceptable level of toxicity.

Introduction

Primary hepatocellular carcinoma (HCC) is one of the most common malignant diseases encountered in parts of Africa and the Far East, including Korea [3, 6]. In Korea, 15 deaths from hepatoma per 100,000 population occur annually; this accounts for 6.7% of all cancer deaths [6]. Of the various solid tumors, hepatoma is perhaps the most difficult cancer to treat in Korea because surgical resection is limited by the advanced stage of the disease at the time of diagnosis and by the high incidence of concurrent cirrhosis.

The prognosis for unresectable hepatoma is dismal, with the median duration of survival being less than 4 months in Yonsei Cancer Center. Following systemic chemotherapy, only 24% of patients have achieved a partial response or stable disease, the median duration of survival being 20 weeks for the responders [4]. Treatment with intra-arterial injection of radioiodinated fatty acid esters ([^{131}I]-lipiodol) results in a reduction in tumor size in 80% of patients when the tumor measures less than 5 cm in diameter; this response rate decreases to only 25% when the tumor is larger than 6 cm in diameter [14]. Therefore, there is no established, effective treatment for unresectable HCC, especially for large hepatomas measuring more than 10 cm in diameter.

Hyperthermia has been used in cancer treatment over the past few decades as an adjuvant to radiotherapy and

* Presented at The Second International Symposium on Treatment of Liver Cancer. Taipei, 3-4 February 1991

Correspondence to: Byung Soo Kim, Division of Cancer Chemotherapy, Yonsei Cancer Center, Yonsei University College of Medicine, C. P. O. Box 8044, Seoul, Korea

Table 1. Patients' characteristics

Number of enrolled patients	30
Number of evaluable patients	30
Sex (M/F):	
M	25
F	5
Age (years):	
Range	29–70
Median	53
Performance status:	
ECOG 1	25
ECOG 2	5
Tumor location:	
Right lobe	25
Left lobe	5
Tumor size (cm):	
5–10	12
10–15	8
>15	10
Type of tumor:	
Single massive	14
Diffuse infiltrative	10
Multinodular	6
Serum αFP:	
Positive	20
Negative	10
Liver cirrhosis:	
Present	18
Absent	12
Abdominal lymphadenopathy:	
Present	6
Absent	24
Portal vein thrombosis:	
Present	8
Absent	22
Ascites:	
Present	4
Absent	26
Child's classification[a]:	
A	13
B	14
C	3
HBsAg:	
Positive	17
Negative	13

[a] A: albumin, >3.5 g/dl; bilirubin, <2 mg/dl; no ascites; no hepatic encephalopathy. C: albumin, <3 g/dl; bilirubin, >3 mg/dl; massive ascites or hepatic encephalopathy. B: all others
HBsAg, Hepatitis B surface antigen

chemotherapy. Since the installation of a radiotherapy (RF) capacitive-heating machine in our institute in 1985, unresectable HCC has been treated with hyperthermia combined with various treatment modalities such as systemic chemotherapy, transhepatic arterial embolization, external radiotherapy, and internal radiotherapy using [^{131}I]-lipiodol. In a pilot study of combined treatment with external radiotherapy and hyperthermia, a remarkable tumor response was observed in several cases [12].

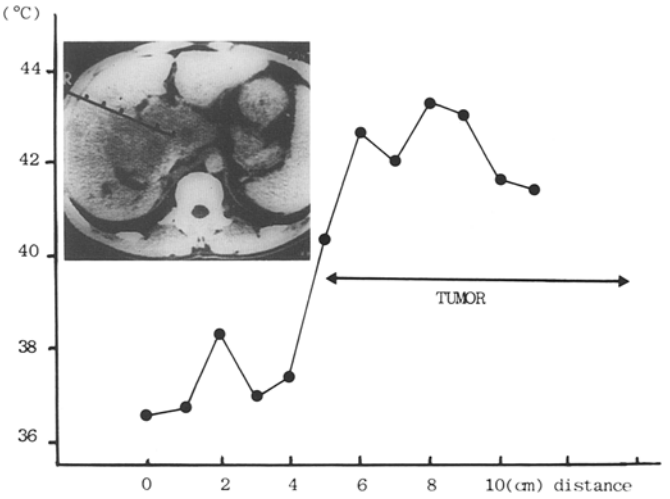

Fig. 1. Temperature distribution as a function of the depth under the skin

Therefore, we designed a phase II trial of external radiotherapy combined with hyperthermia for the treatment of unresectable HCC so as to evaluate the efficacy of this combined regimen. Herein we report the results we obtained in 30 unresectable HCC patients who were treated during this study.

Patients and methods

Patients. A total of 30 subjects with HCC that was unresectable due either to its advanced stage or to associated cirrhosis were entered in the study between April 1988 and July 1988. The diagnosis of HCC was made either histologically or on the basis of a combination of tumor marker (αFP), computerized tomographic (CT) scan, and angiographic findings that were compatible with HCC. The study population included 25 men and 5 women ranging in age from 29 to 70 years (median, 53 years). The performance status was ECOG 1 in 25 patients and ECOG 2 in 5 subjects. As measured by CT scan, the largest tumor diameter exceeded 5 cm in all patients and 10 cm in 18 subjects (60%). Liver cirrhosis was also present in 18 patients (60%), and αFP levels were elevated in 20 subjects (66.7%). According to Child's classification, there were 13, 14, and 3 patients in classes A, B, and C, respectively (Table 1).

Treatment protocol. External radiotherapy was carried out five times a week at 180 cGy/day by conventional fractionations using a 10- or 4-MV linear accelerator. A total tumor dose of 3060 cGy was delivered to an involved field over a period of 3.5 weeks. The radiation field was individually designed to include the tumor mass along with generous margins (upper and lateral margins, 2 cm; lower margin, 3–4 cm) using AP/PA parallel opposing portals or three portals (e.g., AP/PA parallel opposing portals and one lateral portal).

Hyperthermia using 8-MHz capacitive-heating devices, i.e., Thermotron RF-8 (Yamamoto Vinyter Co., Japan) and Cancermia (Green Cross Medical Corp., Korea), was performed twice a week for a total of six sessions. Each hyperthermic session was started within 30 min of the radiotherapy and was continued for 30–60 min in all cases. The principle of RF heating has been reported elsewhere [8]. To prevent overheating and burning of the skin, the circulating 0.4% NaCl solution between the heat exchanger and the electrodes was maintained at a temperature of 5°–10° C.

Measurement of the tumor temperature during hyperthermia was done with the patient's consent by inserting a thermocouple (RF-filtered,

Table 2. Response rates of the patients

Response	Number of patients
Subjective:	
Improvement	22 (78.6%)
No change	5 (16.7%)
Aggravation	1 (4.7%)
Objective:	
Partial response	12 (40.0%)
Stable disease	14 (46.7%)
Progressive disease	4 (13.3%)

Complete response, Complete disappearance of all objective evidence of disease; partial response, decrease of 50% or more in the volume of the tumor with no new lesions or 50% or more tumor necrosis as determined from CT scans; Stable disease, any decrease in tumor size short of a partial response or the lack of any evidence of progressive disease; Progressive disease; increase of more than 50% in tumor size as measured in a similar fashion or the appearance of new lesions

copper-constant microthermocouple; Sensortek Inc., Type IT-18, New Jersey) into the tumor mass under ultrasonographic guidance for patients who had no bleeding tendency. If temperature measurement could not be performed due either to the patient's refusal or to an associated tendency toward bleeding, hyperthermia was conducted by applying the data obtained from the heating conditions (heating power in watts) in patients in whom the temperature was measured. The temperature distribution was measured by pulling the thermocouple out of the tumor to a constant distance (1 cm) along its track just before the end of the heating procedure (Fig. 1).

Assessment of the treatment results. The tumor response was assessed after completion of the treatment. The subjective response was evaluated according to the change in subjective symptoms and performance status. The objective response was assessed by the change in the tumor size as measured by CT scan.

Follow-up patients. The patients were followed from the 1st day of treatment until the end of the study or death.

Follow-up of αFP and liver function. The αFP level and liver-function tests, including albumin, total bilirubin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and alkaline phosphatase (ALK. PHOS.), were consecutively examined at 1 week before the start of treatment (pretreatment), in the middle of the treatment (during treatment), and immediately following and 1 month after the end of treatment (posttreatment).

Statistical analysis. The statistical significance of differences was evaluated using Student's *t*-test, Fisher's exact test, and the chi-square test. Survival analysis was performed by Kaplan-Meier's method.

Results

Tumor response

All 30 of the enrolled patients were evaluable. Symptomatic improvement was observed in 22 of 28 patients who had distressing symptoms such as abdominal pain; hence, the subjective response rate was 78.6%. Among the objective response, no complete response was observed. A partial response was achieved in 12 patients (40%), including 6 who showed a reduction of over 80% in the size of their lesions relative to the initial tumor volume. Another 14 patients showed stable disease, and the remaining 4 subjects had progressive disease (Table 2).

Table 3. Comparison of tumor response as a function of the prognostic factors

Factor		Number of patients	Number of partial responses
Sex (M/F)	M	25	10 (40%)
	F	5	2 (40%)
Age (years)	≤50	10	5 (50%)
	>–50	20	7 (35%)
Tumor location	Right lobe	25	8 (32%)
	Left lobe	5	4 (80%)
Tumor size	5–10 cm	12	7 (58%)
	10–15 cm	8	2 (25%)
	>15 cm	10	3 (30%)
Tumor type	SM	14	10 (71%)
	DI	10	2 (20%)
	MN	6	0 (0)
Serum αFP	Positive	20	8 (40%)
	Negative	10	4 (40%)
Cirrhosis	Present	18	6 (33%)
	Absent	12	6 (50%)
Child's classification	A	13	7 (54%)
	B	14	4 (29%)
	C	3	1 (33%)
Abdominal lymphadenopathy	Present	6	1 (17%)
	Absent	24	11 (46%)
Portal vein thrombosis	Present	8	3 (38%)
	Absent	22	9 (41%)
Ascites	Present	4	0 (0)
	Absent	26	12 (46%)
HBsAg	Positive	17	7 (41%)
	Negative	13	5 (39%)

SM, Single massive; DI, diffuse infiltrative; MN, multinodular; αFP, alpha-fetoprotein; HBsAg, hepatitis B surface antigen
* $P < 0.005$

Factors affecting the tumor response

Among the various factors influencing the response to treatment, the morphological type of the tumor appeared to be the most important factor; the response rates were 71.4% for the single massive type, 20.0% for the diffuse infiltrative type, and 0 for the multinodular type ($P < 0.005$). Tumors in the left lobe responded somewhat better (80%) than did those in the right lobe (32%), with marginal significance ($P = 0.06$). Groups with a tumor diameter of less than 10 cm, Child's class A, and a lack of abdominal lymphadenopathy and ascites showed some tendency toward a better tumor response. Other factors such as sex, age, association with cirrhosis or portal vein thrombosis, and positivity for αFP and hepatitis B virus surface antigen did not show any correlation with the tumor response (Table 3).

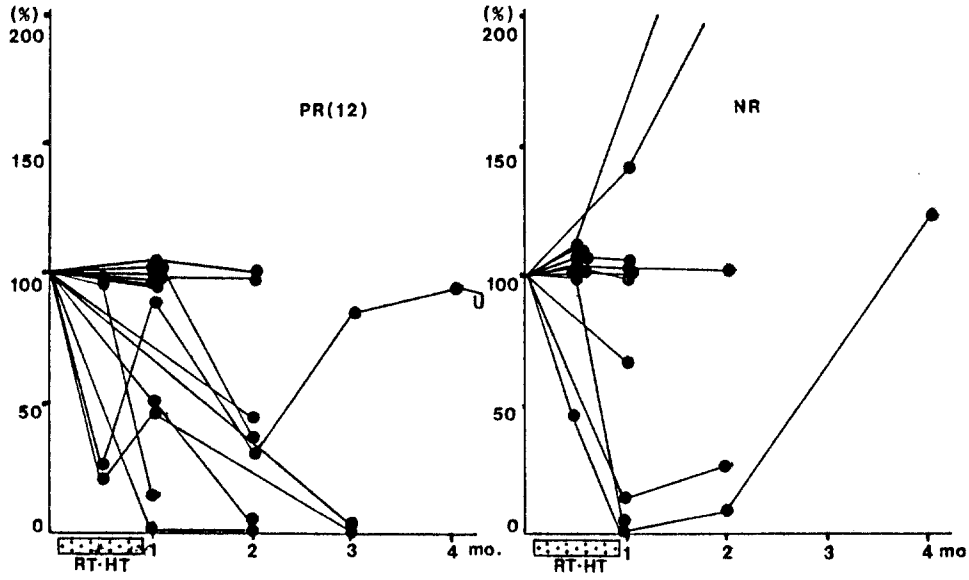

Fig. 2. Serial changes in αFP levels after treatment (24 patients). *RT*, Radiotherapy; *HT*, hyperthermia; *PR*, partial response; *NR*, no response; *mo*, months

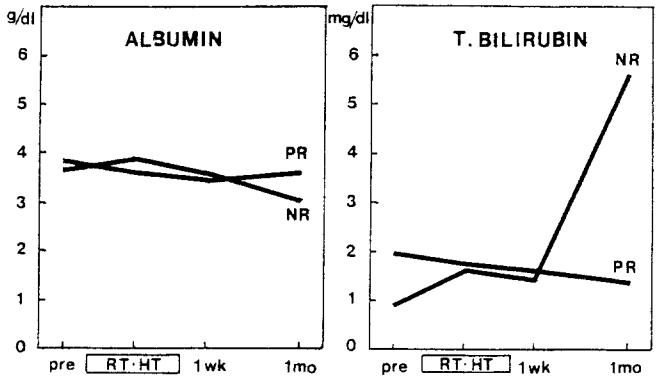

Fig. 3. Serial changes in levels of albumin and total bilirubin (*T. BILIRUBIN*) as liver-function parameters. *PR*, Partial response group (12 patients); *NR*, nor response group (18 patients); *mo*, month; *wk*, week

Serial changes in αFP and liver-function parameters

The αFP level was checked serially in 24 patients. The ratio of the αFP values before and after treatment was plotted. Whereas we observed a stable or decreasing tendency for the αFP level in the partial responders (12 of 24 patients), we noted a stable or increasing tendency for the αFP value in the nonresponders (2 patients; Fig. 2).

In regard to the liver-function tests, the partial responders showed SGOT and SGPT values that increased sharply during the treatment period and then returned to pretreatment levels soon after the end of the treatment. Alkaline phosphatase levels also decreased soon after the end of treatment, but albumin and bilirubin values showed no change. In the nonresponders, SGPT and alkaline phosphatase values showed no change, whereas the albumin levels decreased and the bilirubin and SGOT values increased (Figs. 3, 4; Table 4).

Survival

The overall 1-year survival value was 34% (Fig. 5). The 1-year survival value tended to be greater in the partial responders (50%) than in the nonresponders (22%; $P = 0.09$). The median duration of survival was longer in the partial responders (11 months) than in the nonresponders (5 months; $P < 0.05$; Fig. 5).

Side effects

The most common side effect encountered during the hyperthermia was heat sensation or pain (16 patients, 53.3%), particularly over the skin near the edge of the electrode. Fever (5 subjects, 16.7%), superficial first-degree burns (2 patients, 6.7%), and nausea and vomiting (2 subjects, 6.7%) were common complications of mild severity that

Table 4. Serial changes in liver-function parameters

Parameter	Pre-treatment	During treatment	At completion of treatment	1 month post-treatment
SGOT (IU/l)	91.0±66.2	137.5±73.0	94.8±50.7	105.3±84.6
SGPT (IU/l)	46.6±19.9	79.4±61.4	46.0±31.3	46.6±36.1
Alkaline phosphatase (IU/l)	184.2±75.6	193.7±82.4	151.8±45.8	169.0±41.9
Albumin (g/dl)	3.7± 0.5	3.7± 0.7	3.5± 0.5	3.2± 0.5*
Bilirubin (mg/dl)	1.4± 1.2	1.6± 0.9	1.5± 0.7	3.8± 3.7*

Data represent mean values ± SD
* $P < 0.05$ as compared with the pretreatment value

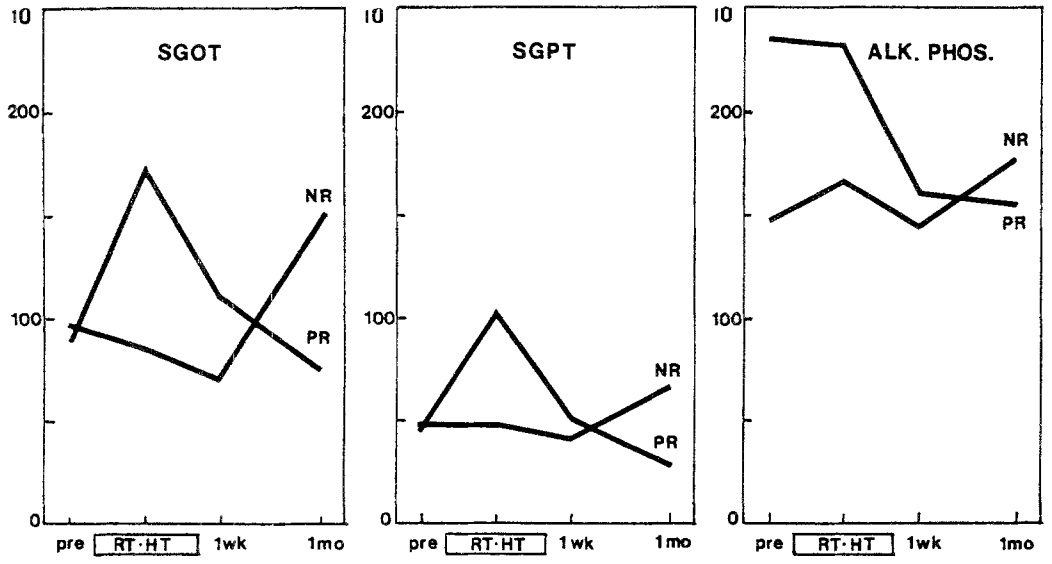

Fig. 4. Serial changes in SGOT, SGPT, and alkaline phosphatase (*ALK. PHOS.*) levels as liver-function parameters. *PR*, Partial response group (12 patients); *NR*, no response group (18 patients); *mo*, month; *wk*, week

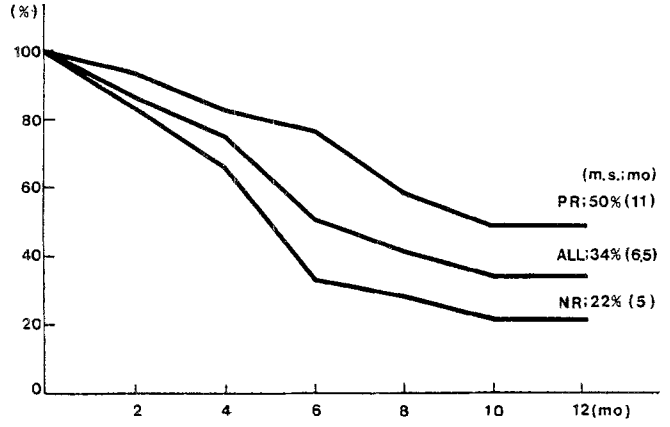

Fig. 5. Overall survival curves generated for the patients. *PR*, Partial responders; *ALL*, all patients; *NR*, nonresponders; *m. s.*, median duration of survival (shown in parentheses); *mo*, months

were controllable without the need for hospitalization or intensive medical care.

Causes of death

Of the 30 patients treated, 11 (36.7%) died, 5 of hepatic failure, 2 due to distant metastasis, 2 of bleeding, and 2 due to unknown causes. Distant metastases had developed in five subjects and involved the brain in one patient and the lung in four others. Among the 11 expired patients, 4 died immediately after completion of the treatment regimen; all 4 of these patients had a large tumor (≥ 15 cm) and associated liver cirrhosis of Child's class B (Table 5).

Representative cases

Case 1. A 56-year-old man was admitted with abdominal pain and an epigastric mass. Abdominal CT examination revealed a huge mass (6.5 × 6.5 × 7 cm) with central necrosis (Fig. 6A). Needle-aspiration biopsy of the mass confirmed it to be a hepatocellular carcinoma. As transarterial embolization failed due to the hypovascularity of the tumor, only lipiodol was given. After combined treatment with radiotherapy and hyperthermia, a partial response was achieved (Fig. 6B). We performed a left lobectomy and removed a well-encapsulated cystic mass measuring 6 × 4 cm (Fig. 6C). The pathological findings in the specimen included marked pleosis and prominent nuclear pleomorphism, which suggested the tumor-killing effect of the treatment.

Case 2. A 70-year-old man was admitted to our institute with a huge epigastric mass and abdominal pain. Abdominal CT examination revealed a huge mass in the left lobe (13 × 10 × 13 cm) (Fig. 7A). The serum αFP level was 12,800 ng/ml. Four courses of systemic chemotherapy with the FAM (5-fluorouracil, Adriamycin, mitomycin) regimen achieved a stable disease state. We then tried our

Table 5. Summary of the patients who died within 2 months

Age (years) sex (M/F)	ECOG PS	Tumor size (cm)/ type	Cirrhosis	Child's class	RT field (cm)	Response	Cause of death
56/M	1	8 × 12 × 15/SM	+	B	16 × 20	PD	HF
52/M	1	8 × 15 × 13/DI	+	B	18.5 × 17.5	PD	HF
42/M	1	15 × 16 × 24/SM	+	B	16.5 × 27	PD	HF
69/M	1	10 × 16 × 16/SM	+	B	16 × 23	PR	Bleeding[a]

[a] Upper gastrointestinal bleeding

RT, Radiotherapy; PD, progressive disease; PR, partial response; SM, single massive; DI, diffuse infiltrative; HF, hepatic failure

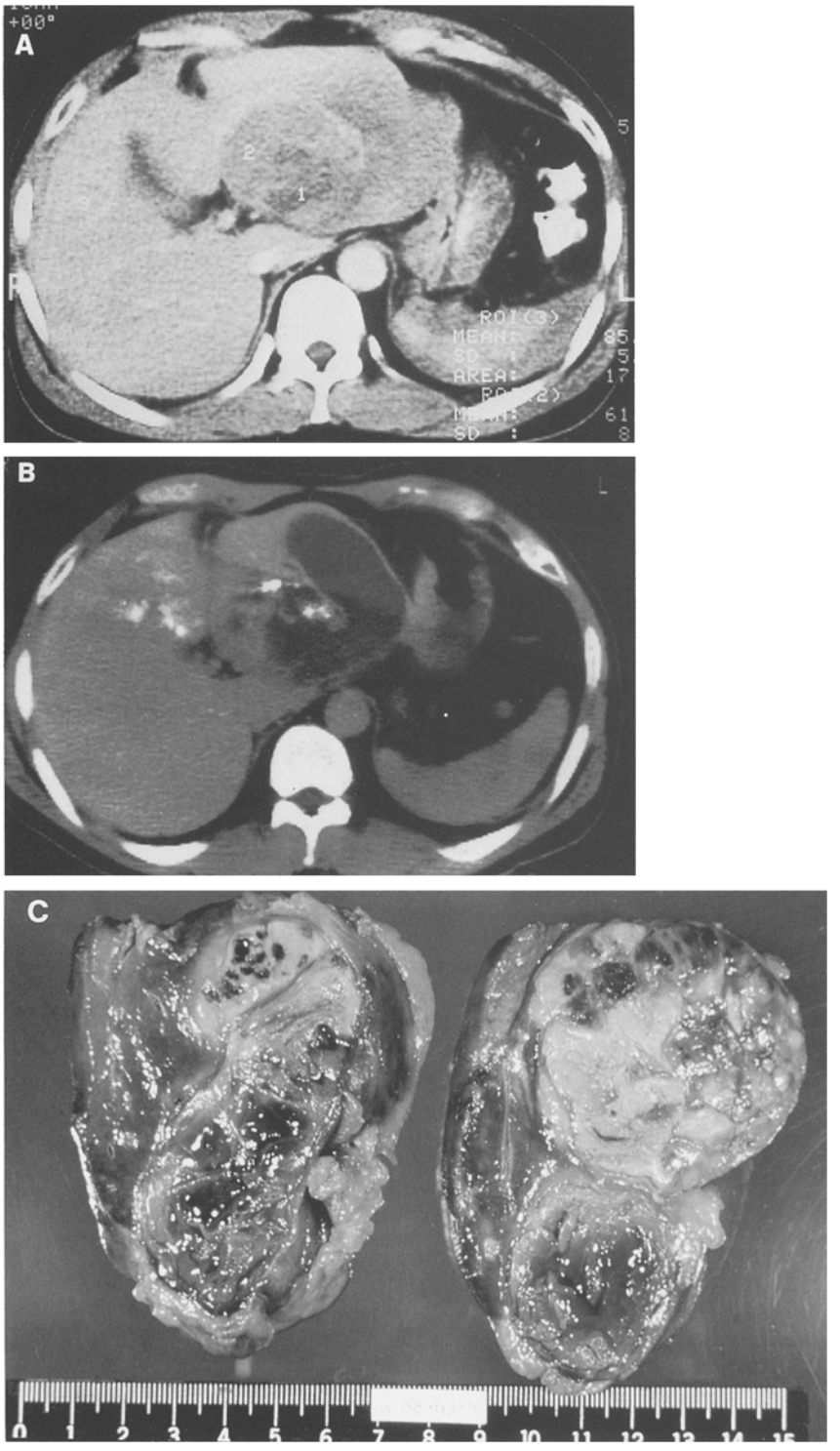

Fig. 6. A A huge tumor mass is visible in the left lobe (6.5 × 6.5 × 7 cm) with central necrosis. **B** A marked necrotic component can be seen in the previous tumor area. A small amount of residual lipiodol is visible in the right upper lobe. **C** Gross findings in the resected mass (6 × 4 cm); the mass is well encapsulated and contains mainly hemorrhagic material

combined protocol of radiotherapy and hyperthermia, which finally induced a nearly complete response of the mass (Fig. 7B). We continued maintenance chemotherapy with 5-fluorouracil for 1 year; 3 months later, a peritoneoscopic biopsy of the previously involved area revealed a focal tumor mass, and the patient died of gastrointestinal tract bleeding. He had survived for 27 months following diagnosis.

Case 3. A 52-year-old man was admitted with epigastric pain and a mass. Abdominal CT examination revealed a huge mass (10 × 11.5 × 12 cm) in the right lobe of the liver, and needle-aspiration biopsy confirmed it to be a hepatocellular carcinoma (Fig. 8A). After completion of the combined radiotherapy and hyperthermia protocol, the follow-up CT scan showed a stable disease state (Fig. 8B). Because the general condition of the patient and the liver functions were good, we decided to treat him with booster radiotherapy of 1440 cGy and three more sessions of hy-

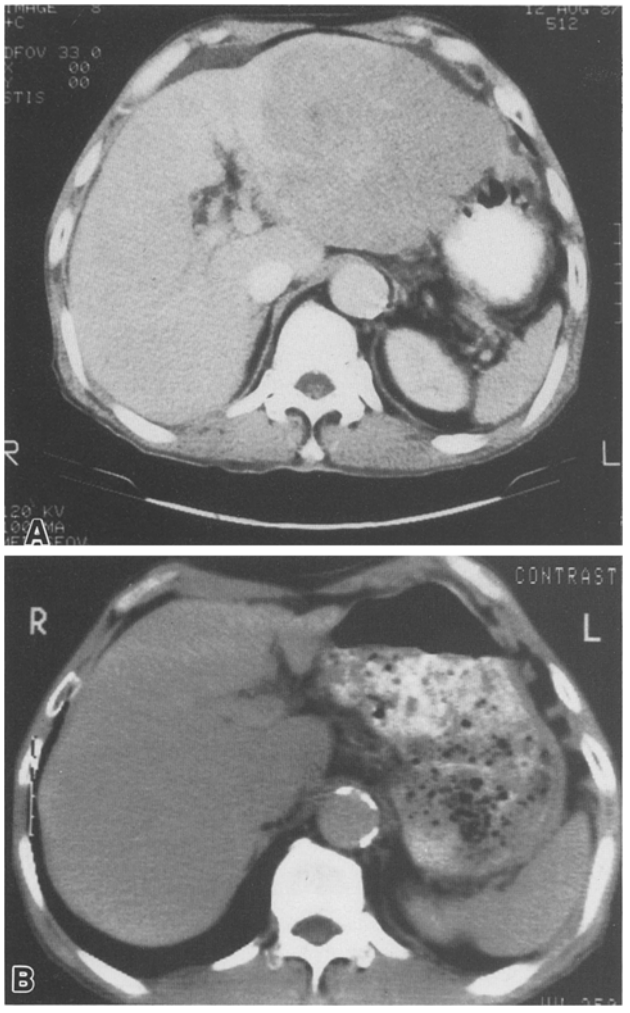

Fig. 7. A A huge mass (13 × 10 × 13 cm) is visible in the left lobe. **B** The mass has responded nearly completely to the treatment

perthermia, resulting in a total radiation dose of 4500 cGy and nine sessions of hyperthermia. After the booster treatment, a partial response was noted, since the diameter of the mass had decreased to 5 cm and it showed central necrosis (Fig. 8C). The necrotic mass remained unchanged for the following 6 months, resulting in an improvement in the patient's general performance status. We then carried out transarterial embolization. After this, the mass was totally converted to a cystic necrotic appearance on the CT scan (Fig. 8D). To date, this patient has survived for 41 months without developing distant metastasis.

Discussion

In Korea, where hepatitis B is endemic, the hepatitis B antigen-positive rate and the cirrhosis-association rate in hepatoma are around 79% and 82%, respectively. Moreover, 90% of patients with hepatitis B antigen have liver cirrhosis or hepatitis as determined pathologically [2]. This high rate of associated cirrhosis makes hepatoma unresectable, even if the tumor is small at diagnosis. Although various therapeutic trials have recently been conducted on the treatment of hepatocellular carcinoma, the prognosis for patients with unresectable tumors remains dismal.

The limited benefit of radiotherapy in HCC is attributable to the low tolerable dose for the whole liver [10, 13]. Therefore, we designed a combined radiotherapy and hyperthermia regimen, assuming that such a combination would enhance tumor lysis at a low radiation dose that might be insufficient to control the tumor. To minimize the possible treatment-related toxicity, the optimal radiation field was determined to include the tumor plus a generous margin, e. g., not the entire liver but an involved field, since most of our patients had a large tumor volume and associated cirrhosis. These factors allowed us to use a smaller total dose of 3060 cGy delivered in daily doses of 180 cGy. Moreover, because our protocol was based on the principle of combination, hyperthermia was planned for the same treatment period as was radiation: two sessions per week carried out at 3-day intervals.

The subjective tumor response was excellent. Abdominal pain, which was the most distressing symptom, was markedly relieved in 22 of 28 patients, resulting in a sensation of well-being. Although no complete response was obtained, the objective response was promising, amounting to a 40% partial response rate; moreover, when cases of stable disease were taken into account, the response rate increased to 56.7%.

Tumor factors that correlated with the prognosis included the tumor volume, resectability, encapsulation, and histological type as well as the presence of concurrent cirrhosis. In our patients who had a large tumor volume and associated cirrhosis, the morphological type was the most significant factor. The reason for the good response obtained in the single massive type might have involved its growth pattern. This type grows in expansile form, is well demarcated, and does not intermingle with adjacent normal tissue [9]. This condition aids in the establishment of hyperthermia/hypoxia in the tumor.

The tumor location, which showed marginal significance, seemed to be related to the technical aspect of capacitive-type heating. In left-lobe tumors, which are usually located along the midline of the body, a pair of parallel opposing electrodes can be applied more suitably without producing an air gap between the two electrodes. In contrast, in right-lobe tumors, which are usually located eccentrically, electrodes are usually unstable and their application produces an air gap just beside the right lateral body wall. This air gap causes a severely hot sensation over the skin, which is one of the factors limiting the delivery of sufficient heat to the tumor. Thus, less heating power might inadvertently be delivered to right-lobe tumors than to left-lobe tumors.

We also noted some tendencies toward differences in the tumor response as a function of the tumor size, the Child's classification, and the presence of abdominal lymphadenopathy and ascites. However, the correlation of these parameters with the response did not reach statistical significance.

Serum αFP is a valuable factor for follow-up after treatment, although the αFP-positive rate in hepatoma is only

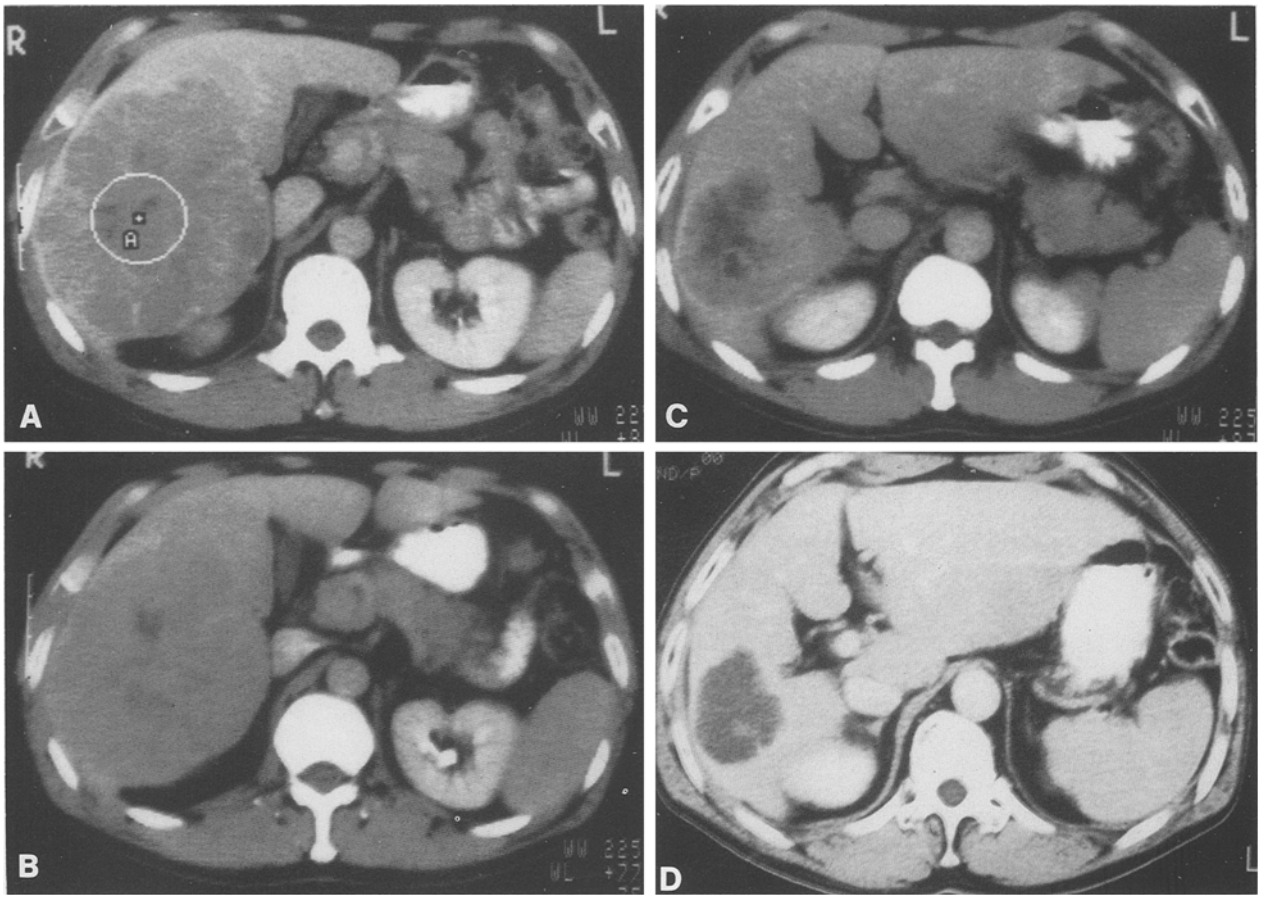

Fig. 8. A At the time of diagnosis, a huge mass (10 × 11.5 × 12 cm) is visible in the right lobe. **B** On completion of the planned radiotherapy and hyperthermia, a stable disease state is apparent. **C** On completion of the booster treatment, the mass has partially responded to the treatment. **D** After transarterial embolization, a cystic change has occurred

around 40%–50% in Korea [5, 7]. In our study, serial measurements of αFP levels disclosed a tendency for the values to be stable or to decrease in partial responders, whereas they tended to remain stable or to increase in nonresponders. Although αFP levels did not accurately coincide with the tumor response observed on CT scans, it might be useful in predicting the tendency for a tumor response.

Both irradiation and hyperthermia of the liver can induce hepatitis [1, 11]. but no report has been published on the occurrence of hepatic dysfunction as a result of combined radiotherapy and hyperthermia. In our study, none of the changes observed in the liver-function parameters of responders were significant except for a transient increase in SGOT and SGPT values and a decrease in alkaline phosphatase levels after the treatment. Significant changes in bilirubin and albumin values were observed in the nonresponders after treatment. Therefore, any significant change in the liver-function parameters would be attributable to progression of the disease itself.

However, the question regarding the treatment's toxicity remains open when we consider the four patients who died immediately after completion of the treatment. The common characteristics of these four patients were a huge tumor size, a large radiotherapy field, and associated cirrhosis of Child's class B. Three of those who showed progressive disease died of hepatic failure, and the remaining partial responder died of upper gastrointestinal bleeding, which might have been related to the aggravated liver cirrhosis. Because we could not perform a liver biopsy or even necropsy, we could not reach any definitive conclusion about liver damage on the basis of the histological findings.

Therefore, it can be suggested that as far as patient selection is concerned, the tumor size and the degree of cirrhosis should be carefully considered, because the function of the uninvolved liver is thought to be a very significant factor. Recently, we began checking the R_{max} values before and after the treatment because this value is believed to represent the reserve liver function more accurately than do the routine parameters. As shown in case 3, we obtained a positive therapeutic effect by increasing the treatment doses. If we can obtain more accurate information about the reserve liver function by using the R_{max} value, there might be some possibility of increasing the response rate by increasing the radiotherapy and hyperthermia doses.

The 34% 1-year survival value and the 6.5-month median duration of survival obtained in the present study are thought to be promising results, since we calculated the survival from the date of treatment initiation rather than from the date of diagnosis. Furthermore, we achieved a

prolongation of survival in the responders. Although the present study was not designed as a randomized trial, we performed transhepatic arterial embolization in a small group of patients whose general condition should have been better than that of the patients who underwent combined radiotherapy and hyperthermia. However, we observed no survival benefit, even in subjects showing a good performance status and a less advanced disease state. In another group that was treated with a combination of transhepatic arterial embolization, radiotherapy, and hyperthermia, the 1-year survival value was 66.8% and the median survival was prolonged to 14 months. On the basis of these data, we are now planning to use this triple-combination treatment in patients with unresectable and less advanced hepatocellular carcinoma.

All of the treatment-related side-effects encountered, such as a hot sensation or pain, fever, first-degree burn, and nausea and vomiting, were self-limiting. Despite the transient changes observed in liver function, the feasibility of radiotherapy was good in all patients, since we used an involved field rather than a whole-liver field. All patients received the planned dose within the scheduled period, regardless of tumor size. However, the tolerability of hyperthermia was lower in patients with large tumors due to the perception of a hot sensation and to general weakness. In these cases we delayed the hyperthermia for a few weeks, waiting for the recovery of liver function, and then continued the remaining schedule. The most frequently observed symptom was a hot sensation of pain, which was related to the heating method (e.g., overheating in the fat-muscle interphase or air gap). To overcome the above problems, we are trying precooling, which means that the treatment area is cooled before the heating procedure is started. Moreover, unusual application of the electrodes, such as an angular arrangement instead of a parallel arrangement in cases of eccentrically located tumors, is under study in our institution.

Although this study is being continued and the results do not yet enable conclusions to be drawn concerning the influence of the combined treatment on survival, the observation that our responders have survived for long periods and have experienced a good quality of life suggests that the treatment exerts a substantial tumor-killing effect as demonstrated in cases 1 and 2. Also, dramatic alleviation of the subjective symptoms was observed in the responders, with acceptable levels of side effects being noted. In conclusion, this combined radiotherapy and hyperthermia regimen seems to be effective in providing local tumor control and pain palliation in patients with unresectable hepatocellular carcinoma.

Acknowledgements. We thank Miss H. Y. Chin for her expert help in the preparation of the manuscript and for her secretarial assistance.

References

1. Ingold JA, Reed GB, Kaplan HS, Bagshaw MA (1965) Radiation hepatitis. AJR 93: 200
2. Jung HC, Kim CY (1988) The serological profiles of hepatitis B virus infection and the prevalence rate of underlying liver cirrhosis in patients with primary liver cancer in Korea. Korean J Gastroenterol 20: 132
3. Kew MC, Geddes EW (1982) Hepatocellular carcinoma in rural southern African blacks. Medicine 61: 98
4. Kim BS, Yoo HS, Park YJ, Loh JJK (1989) Current status and future aspects on treatment of liver cancer. Cancer Chemother Pharmacol 23 [Suppl]: S118
5. Kim CY, Suh DJ, Kim ST, Lee HS (1977) α-Fetoprotein and HBsAg in Korean patients with hepatoma. Korean J Intern Med 20: 229
6. Kim IS, Kim HJ, Kim BS, Oh HC, Lee Y (1984) The cancer registry program in Kangwha county: the first report (July 1982–June 1984). Korean J Epidemiol 6: 100
7. Kwon TS, Lee SM, Park BK, Chung KB, Doh SG (1980) Clinical observation on 252 cases of primary hepatic cancer. Korean J Intern Med 23: 393
8. Loh JJK, Seong JS, Suh CO, Kim GE, Chu SS, Park KR, Lee CG, Kim BS, Kim GS, Seel DJ (1989) Cooperative clinical studies of hyperthermia using a capacitive type heating device, GHT-RF8. Yonsei Med J 30: 72
9. Nakashima T, Okuda K, Kojiro M, Jimi A, Yamaguchi R, Sakamoto K, Ikari T (1983) Pathology of hepatocellular carcinoma in Japan: 232 consecutive cases autopsied in ten years. Cancer 51: 863
10. Phillips R, Murikami K (1960) Primary neoplasms of the liver. Results of radiation therapy. Cancer 13: 714
11. Ries MC, Milligan AJ, Merrick HW, Dobelbower RR (1988) Biochemical and cellular effects of radiofrequency induced interstitial hyperthermia on normal canine liver. Int J Radiat Oncol Biol Phys 14: 529
12. Suh CO, Loh JJK, Seong JS, Roh JK, Kim BS, Park IS, Choi HJ (1980) Effect of radiofrequency hyperthermia on hepatocellular carcinoma. J Korean Cancer Res Assoc 20: 117
13. Wharton JT, Delclos L, Gallager S, Smith JP (1973) Radiation hepatitis induced by abdominal irradiation with the cobalt 60 moving strip technique. AJR 117: 73
14. Yoo HS, Suh JH, Lee JT, Kim KW, Kim DI, Kim BS, Choi HJ, Lee KS (1990) Nodular hepatocellular carcinoma – treatment with intraarterial injection of ^{131}I lipiodol. J Korean Med Sci 5: 75