Combined Radiotherapy and Hyperthermia for Nonresectable Hepatocellular Carcinoma

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Thirty patients with nonresectable hepatocellular carcinoma (HCC) due to either locally advanced lesion or association with liver cirrhosis, treated with combined radiotherapy and hyperthermia between April 1988 and July 1988, at Dept. of Radiation Oncology, Yonsei university College of medicine, were analysed.

External radiotherapy of a total dose of 3060 cGy/3.5 wks was given. Hyperthermia was given twice a week with a total of 6 treatment sessions using 8 MHz radiofrequency capacitive type heating device, i.e., Thermotron RF-8 and Cancermia. In all cases hyperthermia was given within 30 minutes after radiotherapy for 30~60 min.

Temperature was measured by inserting thermocouple into the tumor mass under the ultrasonographic guidance only for those who had not bleeding tendency.

As a result, partial response (PR) was achieved in 12 patients (40%), and symptomatic improvement was observed in 22 patients (78.6%) among 28 patients who had suffered from abdominal pain. The most significant factor affecting the tumor response rate was the type of tumor (single massive: 10/14, 71.4%; diffuse infiltrative: 2/10, 20%; multinodular:0/6, 0%; $p<0.005$). There were not any significant side effects relating to combined treatment. The overall 1 year survival rate was 34%, with 50% in the PR group and 22% in the no response group (NR), respectively. Median survival was 6.5 months and longer for those of PR than of NR (11 mos. vs 5, $p<0.05$).

In conclusion, combined radiotherapy and hyperthermia appeared to be effective in local control and symptomatic palliation of HCC. Further study including a larger number of the patients to confirm its effect in survival and detrimental side effect should be urged.

Key Words: Hyperthermia, Radiotherapy, Hepatocellular carcinoma

Primary hepatocellular carcinoma (HCC) is the major malignant disease in parts of Africa and the Orient including Korea[1~3]. Surgical resection, while representing the best hope of cure, is severely limited by the extent of disease and the high incidence of concurrent hepatic parenchymal disease such as liver cirrhosis[4~7]. Standard fraction radiotherapy alone is rarely effective[8]. Chemotherapy has been an approach for treatment for nonresectable hepatoma however, it produces a minimal response rate and these responses are usually not long lasting[9~12]. Recently, internal radiotherapy using radioisotopes was attempted and some success has been documented, but this has often proven to be a cumbersome technique and clinical application is limited to small sized tumors[13~15].

Therefore, it is our opinion that there is no standard, established, highly effective therapy for nonresectable hepatocellular cancer.

Hyperthermia has been used in the treatment of cancers alone or as an adjuvant to radiation therapy or chemotherapy during the past few decades. Since radiofrequency (RF) capacitive heating machine was introduced in our department in 1985, hyperthermic treatment has been applied to various kinds of malignancies. Nonresectable HCC has been treated with hyperthermia combined with various treatment modalities such as external radiotherapy, systemic chemotherapy, transhepatic arterial embolization, or internal radiotherapy using I-131 lipiodol in our department and remarkable tumor response was observed in several cases, especially in cases treated with hyperthermia and external radiotherapy. These results have been reported elsewhere[16].

So we planned to treat nonresectable HCC with hyperthermia combined with external radiotherapy

Table 1. Time, Method and Criteria of Response Evaluation

Evaluation time	: 1–3 months after the completion of treatment
Subjective response	: by symptom relief or improvement of performance status
Objective response	: by CT scan
Complete Response (CR)	: Complete disappearance of all objective evidence of disease.
Partial Response (PR)	: Decrease of 50% or more in the volume of the tumor with no new lesions or 50% or more of tumor necrosis on CT sean finding
Stable Disease (SD)	: Any decrease in tumor size short of a partial response or lack of any evidence of progressive disease.
Progressive Disease (PD)	: More than 50% increase in tumor size measured in a similar fashion or the appearance of any new lesions.

* SD and PD were considered as no response (NR).

Table 2. Response Rate of 30 HCC Patients

Response		No. of pts (%)
Objective	: PR*	12 (40)
	SD**	14 (46.7)
	PD***	4 (13.3)
Subjective	: improved	22 (78.6)
	no change	5 (16.7)
	aggravation	1 (4.7)

* PR : Partial response
** SD : Stable disease
*** PD : Progressive disease

in order to evaluate tumor response to this treatment, the factors which can predict the tumor response, and any possible toxicities relating to this treatment.

Herein we report on 30 nonresectable HCC patients who were treated by our treatment protocol.

MATERIALS AND METHODS

1. Patient Selection

Thirty patients with nonresectable HCC due either to advanced status or to associated cirrhosis, who were consecutively admitted to our department between April 1988 and July 1988 entered the study. The diagnosis of HCC was made histologically in 12 patients and the remaining 18 patients were diagnosed based on alpha-fetoprotein (AFP) values of >400 ng/ml plus computerized tomographic scan (CT scan) findings compatible to HCC.

There were 25 males and 5 females. Their ages ranged from 29 to 72 years (mean: 53.2). Performance status was assessed according to the Eastern Cooperative Oncology Group (ECOG) scale; 25 patients scored 1 and 5 patients scored 2. The largest diameters of tumors, measured by CT scan, were over 5 cm in all pateints and in 18 patients, tumor sizes were 10 cm or over. Liver cirrhosis was associated in 18 patients (60%) and AFP was elevated in 17 patients (56.7%). According to Child's classification, class A, B, and C were 13, 14 and 3 patients, respectively (Table 3).

2. Treatment

External radiotherapy was given with 180 cGy per day, five times a week fractionations using 10 MV or 4 MV Linear Accelerators with a total tumor dose of 3060 cGy in 3.5 weeks. Radiation fields were individually designed to include the tumor mass with a generous margin using AP/PA parallel opposing portals or AP/PA and one lateral, i.e., three portals.

Hyperthermia using 8 MHz capacitive heating devices, i.e., Thermotron RF-8 (Yamamoto Vinyter Co., Japan) and Cancermia (Green Cross Medical Corp., Korea), was induced twice a week for a total of 6 sessions. Each hyperthermic session was started within 30 minutes after radiotherapy and continued for 30~60 min in all cases. The principle of RF heating has been reported elsewhere[17]. To prevent overheating and resulting burn over the skin, circulating 0.4% NaCl solution between the heat exchanger and electrodes was maintained at the temperature of 5~10℃.

Measurement of tumor temperature during hyperthermia was done with the patient's consent by inserting a thermocouple (RF-filtered, copper-constantan microthermocouple, Sensortek Inc.,

Table 3. Factors Affecting Tumor Response

Factors		No. of Patients	No. of PR (%)
Sex	: male	25	10 (40)
	female	5	2 (40)
Age	: ≤ 50	10	5 (50)
	> 50	20	7 (35)
Tumor location	: right lobe	25	8 (32)
	left lobe	5	4 (80)
Tumor size (cm)	: > 5–10	12	7 (58.3)
	10–15	8	2 (25)
	15 <	10	3 (30)
Tumor type	: SM*	14	10 (71.4)**
	DI	10	2 (20)
	MN	6	0 (0)
Serum AFP***	: positive	20	8 (40)
	negative	10	4 (40)
Cirrhosis	: present	18	6 (33.3)
	absent	12	6 (50)
Child's class	: A	13	7 (53.9)
	B	14	4 (28.6)
	C	3	1 (33.3)
Abdominal lymphadenopathy	: present	6	1 (16.7)
	absent	24	11 (45.8)
Portal vein thrombosis	: present	8	3 (37.5)
	absent	22	9 (40.9)
Ascites	: present	4	0 (0)
	absent	26	12 (46.2)
HBsAg****	: positive	17	7 (41.2)
	negative	13	5 (38.5)

* SM ; single massive/DI ; diffuse infiltrative/MN ; multinodular. ** $p < 0.005$ (Fisher exact test)
*** AFP : Alpha Fetoprotein
**** HBs Ag : Hepatitis B surface antigen.

Table 4. Side Effects Relating to the Treatment in 30 HCC Patients

Side effects	No. of pts (%)
Localized hot sense or pain	16 (53.3)
Fever	5 (16.7)
1° burn	2 (6.7)
Nausea & Vomiting	2 (6.7)

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

3. Assessment of the Results

AFP levels and liver function test including albumin, total bilirubin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and alkaline phosphatase were consecutively examined 1 week before the start of

treatment (pretreatment), in the middle of the treatment (during treatment), and immediately and 1 month after the treatment finished (posttreatment and 1 mo. F/U), respectively. The statistical significance of the differences in liver function parameters was determined by the Student's t-test.

Assessment of tumor response was made 1~3 months after completion of the treatment. Subjective response was assessed by the change in subjective symptoms and performance status. Objec-

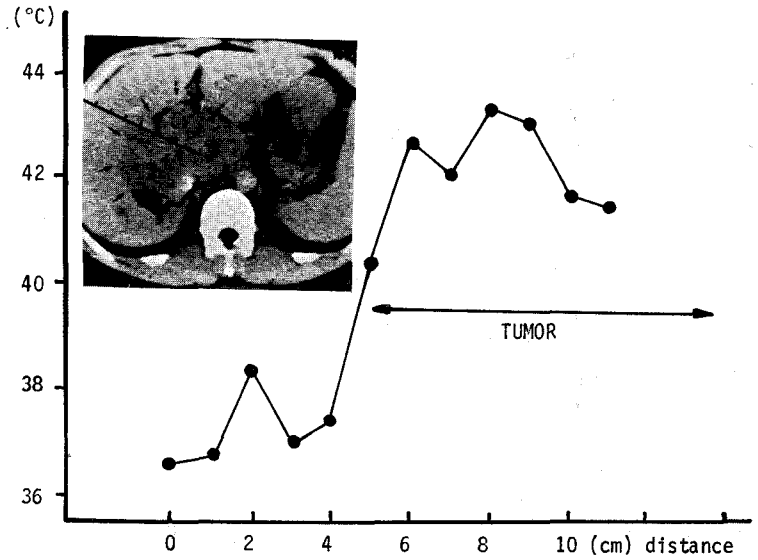

Fig. 1. Temperature distribution along the distance from skin shows higher temperature in tumor than in normal liver parenchyme. In the above CT scan, small arrows indicate tumor and black line is the track of thermocouple.

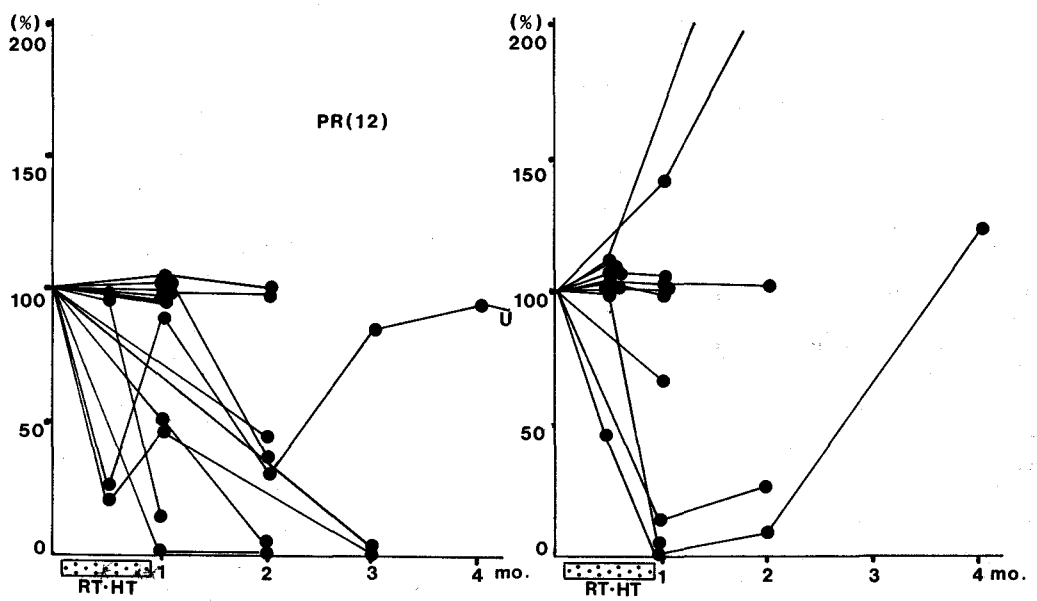

Fig. 2. Serial changes in AFP following treatment (24 pts). AFP: Alpha Fetoprotein RT: Radiotherapy HT: Hyperthermia PR: Partial response NR: No response

tive response was assessed by the change in tumor size measured in CT scan. Criteria of the objective response is listed in Table 1.

The statistical significance of the possible factors affecting the tumor response to the treatment, which are listed in Table 3, was determined by the Fisher's exact test.

All 30 patients were followed until the time of reporting. Estimated curves for survival were plotted from the first day of the treatment by the method of Kaplan and Meier. The statistical significance of survival curves of partial response (PR) and no response (NR) patients and their median survivals were determined according to the chi-square test.

RESULTS

1. Tumor Response

As shown in Table 2, PR was achieved in 12 patients (40%), which includes 6 patients with tumor shrinkage over 80% of initial tumor volume. Another 14 patients showed stable disease and 4 patients, progressive disease.

Symptomatic improvement was observd in 22 patients among 28 patients who had distressing symptoms such as abdominal pain; hence, subjective response rate was 78.6%.

2. Factors Affecting the Tumor Response

Among the various factors, morphological type of the tumor appeared to be the most significant one (response rate of single massive: 10/14, 71.4%; of diffuse infiltrative: 2/10, 20%; and of multinodular: 0/6, 0%, $p<0.005$). Regarding the location of the tumor, tumors in the left lobe showed a better response rate (4/5, 80%) than in the right lobe (8/25, 32%) and the difference appeared to be marginally significant ($p=0.06$). Although statistically not significant, longest diameter of the tumor below 10 cm (response rate of 5~10 cm; 58.3%, 10~15 cm; 25%, and>15 cm; 30%), Child's class A compared to B or C (A: 53.9%, B: 28.6%, C: 33.3%) and absence of abdominal lymphadenopathy (16.7% vs 45.8%) and ascites (0% vs 46.2%) were associated with better tumor response. Other factors such as sex, age, cirrhosis, portal vein thrombosis, and positivity of AFP and HBsAg had no relation with tumor response as shown in Table 3.

3. Serial Changes in AFP and Liver Function Parameters

Serial AFP levels were followed in 24 patients and the percentages of AFP values (after/before treatment×100) were plotted. While the AFP values tended to be unchanged or to decrease after treatment in the PR group (12 out of 24), these values showed no change or increasing tendency (2 patients) in the NR patients (Fig. 2).

With regard to the liver function test, in the PR group, SGOT and SGPT levels increased sharply during the treatment period and then returned to pretreatment levels just after the treatment, alkaline phosphatase decreased just after the treatment, but albumin and bilirubin showed no significant changes. In the NR group, albumin decreased, bilirubin and SGOT increased, while SGPT and alkaline phosphatase showed no significant change (Fig. 3, 4).

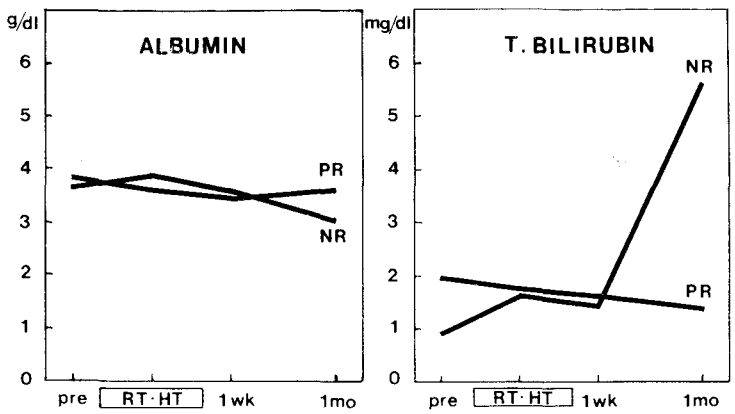

Fig. 3. Serial changes of albumin and total bilirubin among liver function parameters.
PR: Partial response group (12 pts) NR: No response group (18 pts)

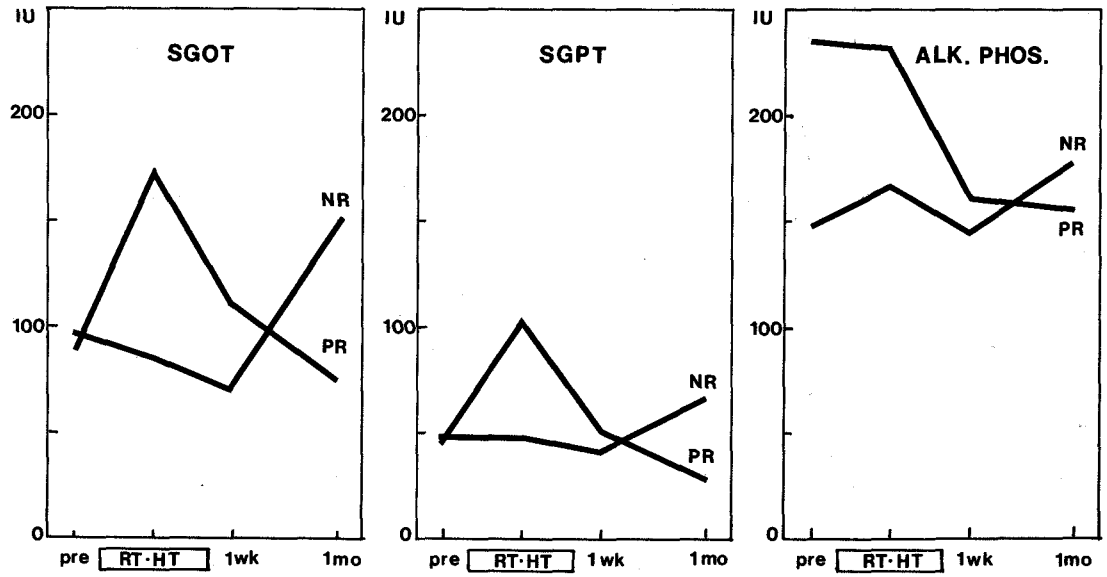

Fig. 4. Serial changes of SGOT, SGPT, and alkaline phosphatase among liver function parameters. PR: Partial response group (12 pts) NR: No response group (18 pts)

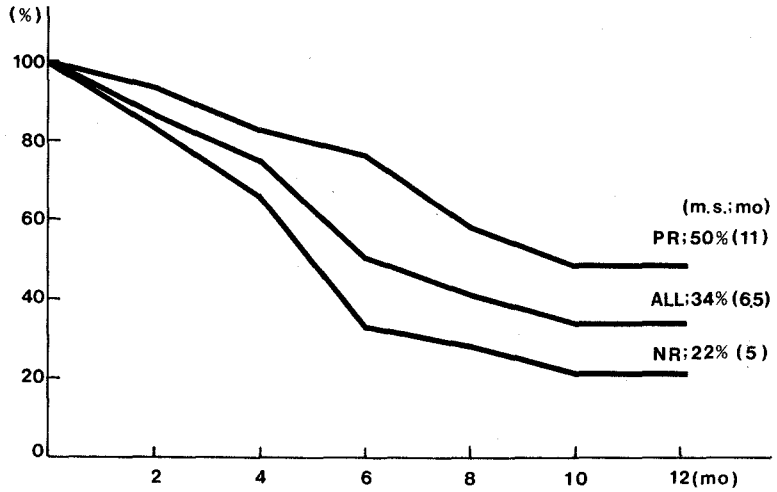

Fig. 5. Survival curves of 30 Hepatocellular Carcinoma Patients after Radiotherapy and Hyperthermia. PR: Partial response group (12 pts), NR: No response group (18 pts)

4. Side effects

The most common complaint during the heat treatment was a hot sensation or pain, particularly over the skin near the edge of the electrode. As shown in Table 4, fever, superficial first degree burn, and nausea and vomiting were observed. But there were no significant toxicities requiring hospitalization or intensive medical care.

5. Survivals

The Kaplan-Meier survival curves are shown in Fig 5. The overall 1 year survival rate was 34%. Comparison of the survival of the PR group (50%) and NR group (22%) showed that the difference

Table 5. Summary of the Patients Who Died Within 2 Months

No.	Age/Sex	ECOG	Tumor Size(cm^3)/Type	Cirrhosis	Child's class	RT field(cm^2)	Response	Cause of death
1.	56/M	H1	8x12x15/SM	+	B	16x20	PD	H.F.*
2.	52/M	H1	8x15x13/DI	+	B	18.5x17.5	PD	H.F.
3.	42/M	H1	15x16x24/SM	+	B	16.5x27	PD	H.F.
4.	69/M	H1	10x16x16/SM	+	B	16x23	PR	Bleeding**

* Hepatic Failure ** Upper gastrointestinal bleeding

was only at borderline significance ($p=0.09$), even though the median survival was longer for those of PR than of NR (11 mos. vs 5 mos., $p<0.05$).

DISCUSSION

Although various therapeutic efforts have recently been made for the treatment of hepatocellular carcinoma, the prognosis of nonrescetable HCC is still dismal[9,18~20].

One of the cancer treatment modalities, radiation, 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. This conclusion is derived from retrospective reviews chiefly of patients from Memorial Hospital and Stanford University[21~24]. Given these restrictions on the dose of radiation that can be safely administered, it can be appreciated why there has been little enthusiasm for radiation as a sole modality.

Hyperthermia as a cancer therapy has the rationale summarized as follows:

1) heat kills cells exponentially as a function of heat at temperature above 42℃[25], 2) heat selectively kills S-phase and hypoxic cells which are known to be radioresistant[26,27], 3) heat interacts synergistically with ionizing radiation and certain chemotherapeutic agents[27,28] and 4) differences in the vasculature in tumors versus normal tissues must lead to a degree of preferential heating and selective biologic effects in tumor tissues[30,31].

Therefore, we attempted combined radiotherapy and hyperthermia to the HCC assuming that such combined treatment would enhance tumolysis in relatively low radiation dose insufficient to control the tumor. Regarding the treatment volume in radiotherapy, whether it should include the entire liver or only the tumor itself with a generous margin was a matter of discussion. Considering that our cases had large tumor volumes usually associated with cirrhosis, and uninvolved hepatic tissue was thought not to have excellent functional ability, the optimum treatment volume was determined to be the tumor plus a generous margin so as to minimize any possible toxicity relating to the treament. The radiation dose was also a matter of discussion. If the tumor is small and confined to one segment of one lobe, a greater radiation dose than usually accepted could be delivered. But the large tumor sizes in our study cases made us to decide to use a smaller dose of 3060 cGy with a daily dose of 180 cGy. The optimum duration and number of hyperthermic treatments are still under argument[32]. Since our treatment protocol was based on the principle of combination, hyperthermia was delivered to the patient in the same treatment period as radiation with 2 sessions per week, each 3 days apart.

In our study, the subjective tumor response was excellent. The most distressing symptom, abdominal pain, was relieved remarkably in 22 out of 28 patients with a sensation of well being. Th objective response was also promising, with a PR rate of 40%. If we consider stable disease as a response, as many other anthors do, the response rate reaches 56.7%. These are thought to be superior results to those of systemic chemotherapy and are also comparable with those of transarterial embolization and intra-arterial chemotherapy[20,33~35].

In many reports, the factors correlated with the prognosis of patients with HCC include tumor volume[36~38], resectability[38,39], encapsulation[40,41], histological type[42~44], and concurrent cirrhosis[39,40,45]. In our study, which includes the patients with nonresectable tumors due either to large tumor volume or to associated liver cirrhosis, the most significant factor appeared to be the morphological type of tumor — the single massive type. A logical explanation would be that this tumor type grows in expansile form, and is well demarcated without being intermingled with adjacent normal tissue[46], hence better conditions for hyperthermia

— hypoxia would exist. The marginally significant factor, the tumor location, seemed to be related to the technical aspect of capacitive type heating. In the left lobe tumor, the target volume would be near the midline of the body. Then it is more suitable to apply a parallelly opposed pair of electrodes because such a stable application usually does not produce an air gap between the two electrodes which causes a localized hot sensation over the skin of that area. On the contrary, in cases of right lobe tumor, particularly an eccentrically located tumor, the application of electrodes is usually unstable and produces an air gap just beside the right lateral body wall. This air gap causes a severe hot sense over that skin, which is one of the limiting factors in delivering sufficient heat to the patient. Therefore, it is presumed that less heat might be delivered to the right lobe tumor than to the left one. To verify such a presumption, a basic study is strongly required. Differences in tumor response were also observed according to tumor size, Child's class, abdominal lymphadenopathy, and ascites, although these were statistically not significant. More extensive study including a larger number of patients is needed to confirm the significance of these factors.

Serum AFP is also valuable for diagnosis and follow-up after the treatment of HCC[47]. Follow-up of serial serum AFP changes disclosed a tendency of no change or decrease in PR patients while that of no change or increase in the remaining non-PR patients. Some authors had reported the outcome of treatment for HCC using the change in AFP[10]. But as shown in our results, it does not accurately coincide with the tumor response seen in CT scan. It can be suggested that the value of serial AFP levels should be used only for predicting the tendency of tumor response.

It has been well known that radiation can induce radiation hepatitis and a resulting increase in alkaline phosphatase in the liver function test[21]. Reports of change in the liver function test after hyperthermia for liver are rare. Recently several authors reported transient increases in SGOT, SGPT and alkaline phosphatase after hperthermia for liver[48]. But there has still been no report about the toxicity resulting from combined radiation and hyperthermia. Fortunately in our study, changes in liver function parameters were not significant except for a transient increase in SGOT and SGPT and a decrease of alkaline phosphatase after the treatment. It is belived that alkaline phosphatase decreased because the initial value was too high (235 ± 77.3 IU/L). On the contrary, a significant increase in bilirubin and decrease in albumin 1 month after the treatment were observed in NR patients. Therefore, it can be thought that this treatment itself would not result in any significant changes in liver function parameters after the treatment is completed. Rather any changes in such parameters would be attributed to the disease progress itself. But the question about treatment toxicity can still be raised, especially if concerning the four patients who died 1 month after the treatment. As summarized in Table 5, the common characteristics among them included a huge tumor mass (the largest diameter was over 15 cm in all), a resulting large radiotherapy field, and associated cirrhosis with Child's B. Three of those who showed progressive disease died of hepatic failure and the remaining one with PR, died of upper gastrointestinal bleeding which might be related to aggravated liver cirrhosis. Because we could not perform a liver biopsy or even necropsy, no definite conclusion about liver damage based on histological change could not be made. It can then be suggested that as far as patient selection is concerned, tumor size and degree of cirrhosis should be carefully considered because the function of the liver uninvolved with the tumor is thought to be a very significant factor. In fact, the above mentioned parameters can not exactly represent liver function because those values can frequently be within normal ranges even though the proportion of normal functioning parenchyme is very small. Now we try to check the Rmax values before and after the treatment, respectively, because that value is believed to represent reserve function of the liver relatively accurately.

Side effects directly related to the treatment such as hot sensation or pain, fever, first degree burn, nausea and vomiting were all self-limited and within an acceptable range. The most frequently observed hot sensation or pain is thought to be related to the heating method. In RF capacitive heating, as mentioned elsewhere, overheating occurs in the fat-muscle interphase because of the difference in conductivity and resistance to RF between the two tissues. That causes hot sense or pain and even subcutaneous fat hardening and necrosis. Due to that, authors who use a similar heating machine to ours agree that RF capacitive heating has limitations in application to fatty areas[49]. Another factor, air gap, which is produced between the two electrodes in cases of eccentrically located tumors, also plays a role in the produc-

tion of hot sensation because RF dose not pass through the air gap but converges on the adjacent body wall. To overcome the above problems, precooling, which means to making the treatment area cool before heating starts, is being tried and an unusual application of electrodes, such as an angular arrangement instead of a parallel arrangement in cases of eccentrically located tumors, is under study in our department.

A one year survival of 34% with median survival of 6.5 months is thought to be a promising result considering that survival was calculated from the day the treatment started and most of our patients elapsed for several weeks to months from the day of diagnosis until visiting our department. Furthermore, a statistically significant difference in median survival was observed between PR and NR patients (11 mos. vs. 5 mos., $p<0.05$).

CONCLUSIONS

Thirty patients with nonresectable hepatocellular carcinoma treated with combined radiotherapy and hyperthermia between April 1988 and July 1988, at the Department of Radiation Oncology, Yonsei University College of Medicine were analysed and the following results were obtained:

1. Partial response was achieved in 12 patients (40%), and symptomatic improvement was observed in 22 patients among 28 who had distressing symptoms (78.6%).

2. The morphological type of the tumor appeared to be the most significant factor affecting the tumor response (response rate of single massive: 10/14, 71.4%; of diffuse infiltrative: 2/10, 20%; and of multinodular: 0/6, 0%; $p<0.005$).

3. Serial AFP levels showed a tendency of being unchanged or decreased in the PR group, while unchanged or increased in the NR group. Changes in liver function paramenters were not significant in the PR group except for a transient increase in SGOT and SGPT but a decrease in albumin and increase of bilirubin were observed in the NR group.

4. All side effects such as hot sensation or pain, fever, superficial first degree burn, nausea, and vomiting were self-limiting.

5. The overall 1 year survival rate was 34% and median survival was 6.5 months. Survivals in the PR and non-PR groups were 50% and 22%, respectively. Median survivals of the PR and NR groups were 11 months and 5 months, respectively, which were statistically significant ($p<0.05$).

In conclusion, combined radiotherapy and hyperthermia appeared to be effective in local control and symptomatic palliation of nonresectable hepatocellular carcinoma. Further study including a larger number of the patients should be urged to confirm its effect on survival and its detrimental effect.

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국문초록 =

절제 불가능한 원발성 간암의 온열 및 방사선 병용 요법

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김 병 수

절제 불가능한 원발성 간암은 여러가지 다양한 치료법의 시도에도 불구하고 그 예후는 극히 불량하다. 이에 본 저자들은 온열요법에 대한 축적된 경험을 바탕으로 1988년 4월부터 7월까지 본과에 내원한 30명의 절제 불가능한 원발성간암 환자들에 대하여 온열 및 방사선 병용요법을 시행하였다.

방사선치료는 일일 조사량 180 cGy씩 3. 5주에 3060 cGy를 조사하였고 온열요법은 8 MHz 유전형온열치료기(Thermotron RF-8, Cancermia)를 사용하여 주 2회씩 총 6회 시행하되 순서는 방사선치료를 먼저 한 후 30분 이내에 온열요법이 30~60분간 시행되었다.

그 결과 부분반응이 12예에서 관찰되었고(40%), 증상의 호전이 28예중 22예에서 관찰되었다(78. 6%). 종양의 반응을 예측할 수 있는 인자로서는 형태학적 유형이 가장 유의하게 나타났다(single massive: 10/14, 71.4%; diffuse infiltrative: 2/10, 20%; multinodular: 0/6, 0%; $p<0.005$). 치료로 인한 심각한 부작용은 관찰되지 않았다. 1년 생존율은 34%였고 정중앙 생존기간은 6.5개월이었다. 부분반응을 보인 환자군의 생존율 및 정중앙 생존 기간은 각각 50%, 11개월로서 반응을 보이지 않은 환자군의 22%, 5개월과 비교해 볼 때 정중앙 생존기간의 차이가 통계적으로 유의하였다($p<0.05$).

결론적으로 온열 및 방사선 병용요법은 절제 불가능한 원발성 간암의 증상호전 및 국소적 치료에 효과가 있는 것으로 생각되며 생존율 및 부작용등에 관해서는 앞으로 연구가 더 진행되어야 할 것으로 생각된다.