The effect of additional radiotherapy after transcatheter arterial chemoembolization in unresectable hepatocellular carcinoma

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ABSTRACT

The effect of additional radiotherapy after transcatheter arterial chemoembolization in unresectable hepatocellular carcinoma

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PURPOSE: In order to determine the effect of additional radiotherapy (RT) after an incomplete transcatheter arterial chemoembolization (TACE) in an unresectable hepatocellular carcinoma (HCC), the treatment results of patients receiving TACE plus RT were analyzed and compared to those treated with TACE alone.

MATERIALS AND METHODS: One hundred and five patients with an unresectable HCC were treated with TACE from January 1992 to December 2002. In 73 of these patients, the TACE was incomplete. Among them, TACE was repeatedly performed in 35 patients (TACE group), the remaining 38 patients were also treated with local RT (TACERT group). The patients were in either stage III or IVa with no evidence of an extrahepatic metastasis, ECOG 2 or less, and Child-Pugh class A or B. The patient characteristics of the two groups were similar. The average frequency of TACE prior to RT was 2 and the RT was started within 7-10 days after the TACE. The median RT dose was 54 Gy.

RESULTS: The 2-yr survival rate was significantly higher in the

TACERT than in the TACE group (36.8 % vs. 14.3%, p=0.001). According to the tumor size, the 2-yr survival rates in the TACERT and TACE group were 63% vs. 42% in 5-7 cm (p=0.22), 50% vs. 0% in 8-10 cm (p=0.03), and 17% vs. 0% in larger than 10 cm (p=0.0002) respectively. Subacute/chronic toxicity in the TACERT group was shown the grade III hepatic (13.2%) and grade II gastrointestinal cases (13.2%), but this was not related to mortality.

CONCLUSION: There was a significantly improved survival rate in the TACERT group of unresectable HCC patients than in the TACE group, particularly in case of tumors with ≥8 cm in diameter. Therefore, radiotherapy in addition to TACE is strongly recommended for patients with an unresectable HCC.

Key words: hepatocellular carcinoma, chemoembolization, radiotherapy

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I. INTRODUCTION

Transcatheter arterial chemoembolization (TACE) has been widely used to treat unresectable hepatocellular carcinoma (HCC) at the initial diagnosis, and is the most common non-surgical treatment in Asian countries[1]. Several nonrandomized studies comparing TACE with the patients' historic data have shown an improvement in the survival time of patients with an unresectable HCC[2-5], particularly in encapsulated tumors smaller than 5 cm[1, 6-8].

However, the tumor cells remain viable in and around the capsule, which is supplied by both arterial and portal blood, and these cells are often responsible for a late recurrence as well as spreading[9, 10]. In fact, randomized controlled trials have failed to show any significant impact on the survival[11-14], suggesting limited effects of TACE even in repeated treatments. To remedy the weakness of TACE, additional treatment such as percutaneous ethanol injection (PEI) might be useful to overcome the limitation of TACE in the treatment of a large HCC[15-17].

The role of radiotherapy (RT) in HCC has long been overlooked because of the low tolerance of the whole liver to

radiation[18]. In earlier trials, low dose radiation on whole liver was combined with chemotherapy, which failed to show satisfactory outcome[19-23]. With the introduction of 3-dimensional conformal radiotherapy (3-DCRT), which enables to deliver higher doses on a targeted portion of the liver, the substantial effect of radiotherapy has been observed by several authors[24-26]. The combined treatment of TACE plus RT has also been attempted, showing a beneficial interaction between RT and chemotherapy[27-32].

Yet, it is uncertain if TACE plus RT is a better treatment modality than TACE alone due to a lack of randomized study comparing the effect of TACE alone with TACE plus RT. In this study, the survival rates and prognostic factors were compared between TACE and TACE plus RT patients retrospectively, and it was attempted to identify a certain special subgroup of patients who might benefit from RT.

II. MATERIALS AND METHODS

1. Patient selection

Between 1992 and 2002, TACE was performed on 105 patients with following criteria at the Yonsei Cancer Center, Yonsei University College of Medicine; The diagnosis of a HCC was based on the characteristic image findings on ultrasound, computed tomography (CT), hepatic angiography, and a serum α-fetoprotein (AFP) level exceeding 400 IU/mL. The tumor was histologically diagnosed by biopsy in all patients with the radiological findings compatible with a HCC but with an AFP level ≤400 IU/mL. The eligibility criteria included the following: (1) the largest tumor dimension ≥5 cm, (2) TACE as the primary treatment, (3) a single tumor. The exclusion criteria were as follows: (1) the presence of an intra- or extrahepatic metastasis, (2) liver cirrhosis of Child class C, (3) a tumor occupying more than two-thirds of the liver, (4) a performance status on the Eastern Cooperative Oncology Group scale ≥3, (5) diffuse infiltrative tumor type and (6) portal vein invasion more than the segmental branch.

Seventy three patients among 105 patients presented an evidence of incomplete TACE shown either on the serial CT or on hepatic angiography after TACE. Among these patients, 38 patients received local radiotherapy after TACE (TACERT group), and 35 patients were treated with TACE alone (TACE group). As shown in Table 1, the patients' characteristics in the two groups were similar.

Table 1. Patients' characteristics

Characteristics	TACE alone		TACE + RT		p-value
	No.	%	No.	%	
No. of patients treated	35	100	38	100	

Age (years)					0.6
Median (range)	57 (40-71)		53 (38-79)		
≤50	16	45.7	15	39.5	
>50	19	54.3	23	60.5	
Gender					0.07
Male	23	65.7	32	84.2	
Female	12	34.3	6	15.8	
Performance (ECOG scale)					0.2
0-1	33	94.3	33	86.8	
2	2	5.7	5	13.2	
α-fetoprotein					0.2
≤400 IU/mL	10	28.5	16	42.1	
>400 IU/mL	23	65.7	18	47.4	
Unknown	2	5.8	4	10.5	
Hypoalbuminemia (<3 g/dL)					0.6
Yes	3	8.6	2	5.3	
No	32	91.4	36	94.7	
Hyperbilirubinemia (>3 mg/dL)					0.5
Yes	2	5.7	4	10.5	
No	33	94.3	34	89.5	
Child-Pugh classification					0.5
A	32	91.4	33	86.8	
B	3	8.6	5	13.2	
Type of tumor					0.4
Massive	19	54.3	17	44.7	
Nodular	16	45.7	21	55.3	
UICC stage					0.6
III	26	74.3	26	68.4	
IVa	9	25.7	12	31.6	
Portal vein thrombosis					0.8
Yes	10	28.6	12	31.6	
No	25	71.4	26	68.4	
Tumor size*					0.5
Median (range)	9.5 (5-17)		10.2 (5-17)		

5-7 cm	12	34.2	8	21.1	
8-10 cm	8	22.9	12	31.6	
>10 cm	15	42.9	18	47.4	
No. of TACE					0.9
Median (range)	2 (1-4)		2 (1-5)		
Additional Treatment†					0.2
(Other than TACE)					
	18	51.4	14	36.8	
	17	48.6	24	63.2	

* Mean value of 3 perpendicular diameters

†Repeated transcatheter arterial chemo infusion (TACI) by adriamycin or cisplatin, and systemic chemotherapy

Abbreviations: ECOG = Eastern Cooperative Oncology Group; AFP = α-fetoprotein; RT = radiotherapy; TACE = transcatheter arterial chemoembolization; UICC = International Union Against Cancer.

2. Transcatheter arterial chemoembolization and radiotherapy

TACE was performed with an infusion of a mixture of an iodized oil contrast medium (Lipiodol™ 4-20 ml) and doxorubicin (Adriamycin™ 20-50 mg), which was followed by gelatin sponge particle (Gelfoam™) embolization. Thirty-eight patients received RT within 7-10 days following TACE using a 10-MV linear accelerator. CT planning was used to determine the radiation volume in each patient, including the tumors with generous margins (2-3 cm). While parallel opposing ports were preferred, a multiport combination of three or more ports was adopted depending on the tumor location. The total dose was determined by the fraction of the non-tumor liver receiving 50% of the isocenter dose. The guideline was as follows: if <25% of the nontumorous liver received 50% of the isocenter dose, the total dose was increased to 59.4 Gy; if 25-50%, the dose was 45-54 Gy; if 50-75%, the dose was 30.6-41.4 Gy; and no treatment was given if >75%. The mean tumor dose was 54 Gy (36-59.4 Gy)

given in daily 1.8 Gy fractions.

3. Evaluation and analysis

During treatment, the patients were monitored weekly with blood count and liver function test. The tumor response was based on the serial CT scans 4–6 weeks after completing the treatment, and then at 1–3 month interval. Complete disappearance of the tumor was considered as a complete response (CR); a decrease in the tumor size ≥50% as a partial response (PR); a decrease in the tumor <50% or no change as stable disease (SD), and progression was considered as a progressive disease (PD). The response rate was calculated for the CR or PR, and SD or PD. The level of AFP was also measured every 1 to 2 months. As a supplementary evidence of tumor response, change in its level was interpreted as PR for a decrease in its initial level of 50% or more, SD for a decrease to <50% or no change, or PD for an increase. Acute toxicity was evaluated weekly during treatment and 1 month after treatment. Subacute or chronic toxicity was defined as that occurring from 1 month after the RT. Survival was estimated from the date of the diagnosis according to the Kaplan-Meier method. Log-rank statistics were used to identify the prognostic factors important for survival. The Cox proportional models using the forward stepwise approach were applied to all the potentially significant variables for the multivariate analysis.

III. RESULTS

1. Tumor response

In 105 patients who received TACE, 73 patients (70%) had viable tumor portion on the serial CT or remaining vascularity on hepatic angiography after TACE. In the TACERT group, an objective response was observed in 25 patients, showing a response rate of 65.8% (Table 2). None of the patients showed CR. SD was observed in 12 patients (31.6%). Only one patient had progressive disease inside the radiation field. The development of an intrahepatic metastasis out of the radiation field was observed in 8 patients. The AFP levels were available in 24 patients of the TACERT group and were analyzed before and after radiotherapy. A PR was observed in 20 patients (83.3%), and 3 patients (12.5%) had PD (Table 3).

Table 2. Tumor response based on CT in the TACERT group

Tumor response	Patients (%)
Response	
Complete response	0 (0.0)
Partial response	25 (65.8)
No response	
Stable disease	12 (31.6)
Progressive disease	1 (2.6)

Table 3. CT response vs. AFP response after radiotherapy

	CT response		
AFP response	PR	SD	PD
PR	13	7	
SD	1		
PD		2	1

NOTE: AFP response; % decreased ≥50%: PR, decreased <50% or no change: SD, increased: PD

2. Factors affecting the survival

The analyses of the prognostic factors were based on the survival from the date of the diagnosis. There were no significant difference in the cause of death between the two groups, which was mainly the result of hepatic failure including hepatic encephalopathy, variceal bleeding, and progression of the tumor itself. On the univariate analysis (Table 4), the tumor size, the presence of hypoalbuminemia, the type of tumor, and the treatment option were significant variables. The tumors were divided into three groups according to the mean tumor size: 5-7 cm, 8-10 cm, and >10 cm. The 2-yr survival rates were 50.0%, 30.0%, and 9.1%, respectively (P=0.003). The survival rate at 2-yr was significantly higher in the TACERT group than in the TACE group (36.8 % vs. 14.3%, p=0.001)(Fig. 1). Patients with hypoalbuminemia had a poorer result, with a 2-yr survival rate of 0% compared with 27.9% for those without hypoalbuminemia (P=0.028). The type of tumor was also found to be a significant factor (P=0.020). On the multivariate analysis (Table 5), the tumor size and treatment option were significant factors affecting survival (P=0.000).

Table 4. Prognostic factors affecting the survival on univariate analysis

Factor	No. of patients	%	Survival rate (2-yr)	p-value
Age (years)				
≤50	31	42.5	19.4	
>50	42	57.5	30.9	0.526
Gender				
Male	55	75.3	27.3	
Female	18	24.7	22.2	0.877
Performance (ECOG scale)				
0-1	66	89.4	84.8	
2	7	9.6	28.5	0.478
α-fetoprotein				
≤400 IU/mL	26	38.8	33.3	
>400 IU/mL	41	61.2	17.5	0.340
Hypoalbuminemia (<3 g/dL)				
Yes	5	6.8	0	
No	68	93.2	27.9	0.028
Hyperbilirubinemia (>3 mg/dL)				
Yes	6	8.2	0	
No	67	91.8	28.4	0.112
Child-Pugh classification				
A	65	89	27.7	
B	8	11	12.5	0.152
Type of tumor				
Massive	36	49.3	11.1	
Nodular	37	50.7	40.5	0.020
UICC stage				
III	52	71.2	28.9	

IVa	21	28.8	19.7	0.927
Portal vein thrombosis				
Yes	22	69.9	18.2	
No	51	30.1	29.4	0.972
Tumor size*				
5-7 cm	20	27.4	50.0	
8-10 cm	20	27.4	30.0	
>10 cm	33	45.2	9.1	0.003
Treatment option				
TACE	35	47.9	14.3	
TACE+ RT	38	52.1	36.8	0.001

Survival was calculated from the beginning of RT according to the Kaplan-Meier method.

Abbreviations as in Table 1.

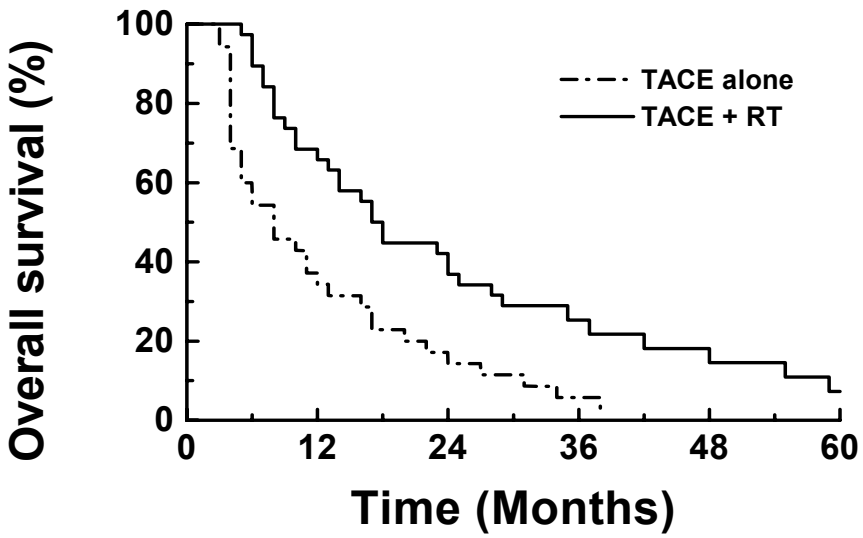

Fig. 1. Overall survival according to the treatment option between TACE alone and TACERT group

Table 5. Prognostic factors affecting the survival on multivariate analysis

Factor	Relative risk	95% confidence interval	p-value
Tumor size	2.828	1.610-4.968	0.000
Hypoalbuminemia	0.438	0.168-1.145	0.092
Type of tumor	0.852	0.500-1.452	0.556
Treatment option	2.812	1.647-4.800	0.000

3. Survival analysis according to tumor size

Since the tumor size and treatment option were identified as significant prognostic factors, further analysis was done according to the tumor size as shown in Table 6. The 2-yr survival rates in the TACERT and TACE group were 63% vs. 42% in 5-7 cm, 50% vs. 0% in 8-10 cm, and 17% vs. 0% in >10 cm. There was no significant survival difference in the patients with tumors 5-7 cm (P=0.22) between the treatment groups. However, the survival rate of the TACERT group was significantly higher than that of the TACE group in tumors with 8-10 cm (p=0.03) and larger than 10 cm (p=0.0002).

Table 6. Survival according to tumor size

	2-yr survival rate (%)		
Tumor size	TACE	TACE+ RT	p-value
5-7 cm	42	63	0.22
8-10 cm	0	50	0.03
> 10 cm	0	17	0.0002

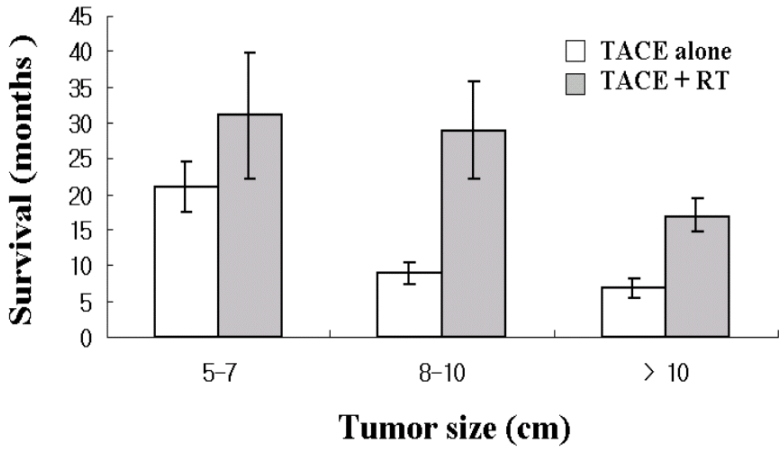

Fig. 2. Survival according to tumor size

4. Toxicity

Fever, abdominal pain, nausea and vomiting were observed in most patients after TACE. These symptoms were self-limited in most patients, lasting no more than 1 week. The other toxicities are summarized in Table 7. In acute toxicity, grade I hepatic toxicity was shown in both groups similarly (20.7% in TACE vs. 15.8% in TACERT). However, in the TACERT group, grade I hematological toxicity (5.4%) was also noted. Subacute and chronic toxicity including radiation induced liver disease (RILD) was observed in 5 patients (13.2%), a gastroduodenal ulcer was observed in 3 patients (7%), and gastroduodenitis in 2 patients (5%). No death was related to the treatment.

Table 7. Toxicity in TACERT group

	Toxicity grade			
	1	2	3	4
Acute				
Hepatic				
Hyperbilirubinemia		2		
Hypoalbuminemia				
Alteration of transaminase	4			
Hematologic				
Leukopenia	1			
Thrombocytopenia	1			
Subacute-chronic				
Hepatic				
RILD*			5	
Gastrointestinal				
Gastric ulcer		2		
Duodenal ulcer		1		
Gastritis		1		
Duodenitis		1		

*Radiation induced liver disease defined as grade 3 or higher toxicity, according to the Common Toxicity Criteria Version 2.0 of the National Cancer Institute, in the absence of documented progressive disease.

IV. DISCUSSION

During the past decade, a number of reports have documented the effect of local RT in HCC, alone or in combination with another modality such as TACE. Matsuura et al.[33] reported a 2-yr survival rate of 36.4% for 22 HCC patients treated with RT alone or in combination with TACE or percutaneous ethanol injection therapy. Cheng et al.[24] reported a 2-yr survival rate of 41% with a median survival time of 19 months for patients treated with local RT with or without TACE. Our previous reports[34] showed a 2-yr survival rate 30.5% in 158 patients treated with local RT. In the present study, the survival rate at 2 years and the median survival time after diagnosis were comparable to reported results.

In this study, the TACERT group had a longer survival time than the TACE group particularly in those with tumors ≥8 cm. Although TACE has been frequently used in the treatment of unresectable HCC, its limitation has also been well known, especially in large tumors. The tumor size is an important prognostic factor in patients with an unresectable HCC receiving TACE, as shown in many other studies[6, 35-37]. Higuchi et al.[35] reported that the rate of necrosis after TACE was no more than 44% when HCCs were larger than 3 cm. The present study also showed that the tumor size was an independent prognostic factor affecting survival. In the TACE group, as the tumor size increased, the survival rates decreased. However in the TACERT group, this relationship was compromised, evidenced by comparable survival rates between 5-7 cm tumors and 8-10 cm tumors (Fig. 2). The greater improvement in the survival rate was shown in the patients with tumors ≥8 cm comparing to those with tumors 5-7 cm, which further emphasizes the efficacy of RT.

Earlier trials adopted whole liver irradiation but used an inadequate radiation dose[19, 22, 23]. Because of the unsatisfactory

results of this low-dose whole liver irradiation, RT has not been seriously considered as an element in the treatment of HCC. Recently, local but not whole liver RT has been attempted by several investigators, who have reported that high radiation doses can be delivered safely to a portion of the liver alone or in combination with other non-surgical treatment modalities.

The 3-DCRT allows much higher doses on focal liver as well as excluding a significant portion of the non-tumor liver from the radiation volume[25, 26]. It provides a good rationale for applying 3-DCRT for HCC in cirrhotic patients. At our institute, local radiotherapy combined with transcatheter arterial chemoembolization (TACE) has been used to treat unresectable HCCs and a substantial tumor response has been achieved[34, 38]. Robertson et al.[39] reported a higher response rate and prolonged hepatic control in their high dose focal radiation group. In the Radiation Therapy Oncology Group report, a high-dose group also showed better results[40].

We previously reported the existence of a dose-response relationship in local radiotherapy for primary HCCs[41]. More recently, Dawson et al.[42] reported that tumor control and survival in intrahepatic cancers could be improved with an increase of RT dose. All these reports highlight the importance of dose escalation to induce tumor regression and ultimately achieve a success in terms of increased survival in HCC.

When the RT dose is escalated, complications should be considered. Since most HCC patients have underlying liver cirrhosis, any liver-directed treatment may cause serious hepatic complication, hepatic failure. Seong et al.[43] established an animal model with clinically relevant liver cirrhosis. Her group showed a significantly higher incidence of lethal liver injury in cirrhotic rats after the combination treatment of RT and 5-Fu. It is suggested that in HCC, protection of the host from the toxicity should be more emphasized in parallel with improvement of tumor response. In this study, a strict criteria of patient

selection was applied, which might have related with relatively low hepatic complication. Since most current treatment schemes adopt combination regimen with chemotherapy, further study is necessary to determine the predictive factors for complication. An indocyanin green retention test at 15min (ICG 15), as an example, has been used in clinics to determine the extent of a surgical resection[44]. It could be similarly applied in case of radiotherapy either to determine the indication for radiotherapy or to predict complications.

There are no reports that have examined the relationship between the CT response and the AFP level after radiotherapy, which is a biochemical tumor marker of a HCC. In this study, the AFP level was measured in 24 patients before and after RT, and the relationship between them was analyzed. Although no statistical significance was observed, the AFP level was lower when CT showed a PR response except in 1 patient. It is expected that biochemical tumor markers of a HCC including the AFP level, might also be used as a supplementary parameter in evaluating tumor response after radiotherapy.

In conclusion, there was a significantly improved survival rate in the TACERT group of unresectable HCC patients than in the TACE group, particularly when their tumors were ≥8 cm. Therefore, radiotherapy in addition to TACE is strongly recommended for patients with an unresectable HCC.

REFERENCES

1. Okuda S: Transcatheter arterial chemoembolization for advanced hepatocellular carcinoma. J Hepatol 1990;11:181-184
2. Matsui O, Kadoya M, Yoshikawa J, Gabata T, Takashima T, Demachi H: Subsegmental transcatheter arterial embolization for small hepatocellular carcinomas: Local therapeutic effect and 5-year survival rate. Cancer Chemother Pharmacol 1994;33:84-88(supp l)
3. Stefanini GF, Amorati P, Biselli M, Mucci F, Celi A, Arienti V et al: Efficacy of transarterial targeted treatments on survival of patients with hepatocellular carcinoma: An Italian experience. Cancer 1995;75:2427-2434
4. Vetter D, Wenger JJ, Bergier JM, Doffoel M, Bockel R: Transcatheter oily chemoembolization in the management of advanced hepatocellular carcinoma in cirrhosis: Results of a western comparative study in 60 patients. Hepatology 1991;13:427-433
5. Bronowicki JP, Vetter D, Dumas F, Boudjema K, Bader R, Weiss AM et al: Transcatheter oily chemoembolization for hepatocellular carcinoma: A 4-year study of 127 French patients. Cancer 1994;74:16-24
6. Ikeda K, Kumada H, Saitoh S, Arase Y, Chayama K: Effect of repeated transcatheter arterial embolization on the survival time in patients with hepatocellular carcinoma. Cancer 1991;68:2150-2154
7. Lin DY, Liaw YF, Lee TY, Lai CM: Hepatic arterial embolization in patients with unresectable hepatocellular carcinoma: A randomized controlled trial. Gastroenterol 1988;94:453-456
8. Okamura J, Horikawa S, Fujiyama T, Monden M, Kambayashi J, Sikujara O et al: An appraisal of transcatheter arterial embolization combined with transcatheter arterial infusion of

chemotherapeutic agent for hepatic malignancies. World J Surg 1982;6:352-357
9. Sakurai M, Okamura J, Kuroda C: Transcatheter chemoembolization effective for treating hepatocellular carcinoma: a histopathologic study Cancer 1984;54:387-392
10. Yu YQ, Xu DB, Zhou XD, Lu JZ, Tang ZY, Mack P: Experience with liver resection after hepatic arterial chemoembolization for hepatocellular carcinoma. Cancer 1993;71:62-65
11. Bruix J, Llovet JM, Castells A, Montana X, Bru C, Ayuso MC et al: Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: Results of a randomized, controlled trial in a single institution. Hepatology 1998;27:1578-1583
12. Pelletier G, Roche A, Ink O, Anciaux ML, Derhy S, Rougier P et al: A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. J Hepatology 1990;11:181-184
13. Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire: A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma [see comments]. N Engl J Med 1995;332:1256-1261
14. Madden MV, Krige JE, Bailey S, Beningfield SJ, Geddes C, Werner ID et al: Randomised trial of targeted chemotherapy with lipiodol and 5-epidoxorubicin compared with symptomatic treatment for hepatoma. Gut 1993;34:1598-1600
15. Koda M, Murawaki Y, Mitsuda A, Oyama K, Okamoto K, Idobe Y et al: Combination therapy with transcatheter arterial chemoembolization and percutaneous ethanol injection compared with percutaneous ethanol injection alone for patients with small hepatocellular carcinoma: a randomized control study. Cancer 2001;92:1516-1524
16. Lencioni R, Paolicchi A, Moretti M, Pinto F, Armillotta N, Di Giulio M et al: Combined transcatheter arterial chemoembolization and percutaneous ethanol injection for the

treatment of large hepatocellular carcinoma: local therapeutic effect and long-term survival rate. Eur Radiol 1998;8:439-444
17. Ki rchhof T, Chavan A, Galanski M: Transarterial chemoembolization and percutaneous ethanol injection therapy in patients with hepatocellular carcinoma. Eur J Gastroenterol Hepatol 1998;10:907-909
18. Lawrence TS, Robertson JM, Anscher MS, Jirtle RL, Ensminger WD, Fajardo LF: Hepatic toxicity resulting from cancer treatment. Int J Radiat Oncol Biol Phys 1995;31:1237-1248
19. Cochrane AM, Murray-Lyon IM, Brinkley DM, Williams R: Quadruple chemotherapy versus radiotherapy in treatment of primary hepatocellular carcinoma. Cancer 1977;40:609-614
20. Dhir V, Swaroop VS, Mohandas KM, Dinshaw KA, Desai DC, Nagral A et al: Combination chemotherapy and radiation for palliation of hepatocellular carcinoma. Am J Clin Oncol 1992;15:304-307
21. Epstein B, Ettinger D, Leichner PK, Order SE: Multimodality cisplatin treatment in nonresectable alpha-fetoprotein-positive hepatoma. Cancer 1991;67:896-900
22. Friedman MA, Volberding PA, Cassidy MJ, Resser KJ, Wasserman TH, Phillips TL: Therapy for hepatocellular cancer with intrahepatic arterial adriamycin and 5- fluorouracil combined with whole-liver irradiation: a Northern California Oncology Group Study. Cancer Treat Rep 1979;63:1885-1888
23. Stillwagon GB, Order SE, Guse C, Klein JL, Leichner PK, Leibel SA et al: 194 hepatocellular cancers treated by radiation and chemotherapy combinations: toxicity and response: a Radiation Therapy Oncology Group (RTOG) study. Int J Radiat Oncol Biol Phys 1989;17:1223-1229
24. Cheng JC-H, Chuang VP, Cheng SH, Huang AT , Lin Y-M, M.D.,Cheng T-I et al: Local radiotherapy with or without transcatheter arterial chemoembolization for patients with unresectable hepatocellular carcinoma. Int J Radiat Oncol Biol

Phys 1989;47:435-442
25. Lawrence TS, Tesser RJ, Ten Haken RK: An application of dose volume histograms to the treatment of intrahepatic malignancies with radiation therapy. Int J Radiat Oncol Biol Phys 1990;19:1041-1047
26. Lawrence TS, Ten Haken RK, Kessler ML, Robertson JM, Lyman JT, Lavigne ML et al: The use of 3-D dose volume analysis to predict radiation hepatitis. Int J Radiat Oncol Biol Phys 1992;23:781-788
27. Le Pechoux C, Akine Y, Tokita N, Sumi M, Churei H, Takayasu K et al. Case report: Hepatocellular carcinoma diagnosed radiologically treated by transcatheter arterial embolization and limited-field radiotherapy. Br J Radiol 1994;67:591-595
28. Yoshikawa M, Ebara M, Ohto M, Miyoshi T: A combination treatment of transcatheter arterial embolization(TAE) and irradiation for hepatocellular carcinoma(HCC): evaluation for therapeutic efficacy in comparison with TAE or irradiation alone. Jpn J Gastroenterol 1990;87:225-234
29. Matsuura M, Ishikawa A, Nakajima N, Itoh K, Matsumoto M: Radical radiation therapy of hepatocellular carcinoma. Nippon Igaku Hoshasen Gakkai Zasshi 1994;54:628-635
30. Guo WJ, Yu EX: Evaluation of combined therapy with chemoembolization and irradiation for large hepatocellular carcinoma. Br J Radiol 2000;73:1091-1097
31. Chia-Hsien Cheng J, Chuang VP, Cheng SH, Lin YM, Cheng TI, Yang PS et al: Unresectable hepatocellular carcinoma treated with radiotherapy and/or chemoembolization. Int J Cancer 2001;96:243-252
32. Seong J, Park HC, Han KH, Lee DY, Lee JT, Chon CY et al. Local radiotherapy for unresectable hepatocellular carcinoma patients who failed with transcatheter arterial chemoembolization. Int J Radiat Oncol Biol Phys 2000;47:1331-1335
33. Matsuura M, Nakajima N, Arai K, Ito K. The usefulness of

radiation therapy for hepatocellular carcinoma.
Hepatogastroenterology 1998;45:791-796
34. Seong J, Park HC, Han KH, Chon CY, Chu SS, Kim GE et al: Clinical results and prognostic factors in radiotherapy for unresectable hepatocellular carcinoma: A retrospective study of 158 patients. Int J Radiat Oncol Biol Phys 2003;55:329-336
35. Higuchi T, Kikuchi M, Okazaki M. Hepatocellular carcinoma after transcatheter hepatic arterial embolization. A histopathologic study of 84 resected cases. Cancer 1994; 73:2259 -2263
36. Hatanaka Y, Yamashita Y, Takahashi M, Koga Y, Saito R, Nakashima K et al: Unresectable hepatocellular carcinoma: analysis of prognostic factors in transcatheter management. Radiology 1995;195:747-752
37. Mondazzi L, Bottelli R, Brambilla G, Rampoldi A, Rezakovic I, Zavaglia C et al. Transarterial oily chemoembolization for the treatment of hepatocellular carcinoma: a multivariate analysis of prognostic factors. Hepatology 1994;19:1115-1123
38. Seong J, Park HC, Han KH, Chon CY, Chu SS, Kim GE, Suh et al. Clinical results of 3-dimensional conformal radiotherapy combined with transarterial chemoembolization for hepatocellular carcinoma in the cirrhotic patients. Hepatol Res. 2003;27(1):30-35
39. Robertson JM, Lawrence TS, Dworzanin LM, Andrews JC, Walker S, Kessler ML et al: Treatment of primary hepatobiliary cancers with conformal radiation therapy and regional chemotherapy. J Clin Oncol 1993;11:1286-1293
40. Order SE, Stillwagon GB, Klein JL, Leichner PK, Siegelman SS, Fishman EK et al: Iodine 131 antiferritin, a new treatment modality in hepatoma: A Radiation Therapy Oncology Group study. J Clin Oncol 1985;13:1573-1582
41. Park HC, Seong J, Han KH, Chon CY, Moon YM, Suh CO: Dose-response relationship in local radiotherapy for hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 2002;54:150-155

42. Dawson LA, McGinn CJ, Normolle D, Ten Haken RK, Walker S, Ensminger W et al: Escalated focal liver radiation and concurrent hepatic artery fluorodeoxyuridine for unresectable intrahepatic malignancies. J Clin Oncol 2000;18:2210-2218
43. Seong J, Han KH, Park YN, Nam SH, Kim SH, Keum WS et al. Lethal hepatic injury by combined treatment of radiation plus chemotherapy in rats with thioacetanide-induced liver cirrhosis. Int J Radiat Oncol Biol Phys 2003;57:282-288
44. Matsumata T, Kanematsu T, Yoshida Y, Furuta T, Yanaga K, Sugimachi K: The indocyanine green test enables prediction of postoperative complication after hepatic resection. World J Surgery 1987;11:678-681

ABSTRACT (IN KOREAN)

절제 불가능한 간세포 암에서 경동맥화학색전술 후 방사선치료 추가의 효과

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목 적: 절제 불가능한 간세포 암에서 불완전한 경동맥화학색전술 후에 방사선치료를 추가하였을 때의 효과를 검증하기 위하여 경동맥화학색전술 후 방사선치료를 시행한 환자와 경동맥 화학색전술만 시행한 환자의 치료 성적을 비교 분석하였다.

재료 및 방법: 1992 년 1 월부터 2002 년 12 월까지 절제 불가능한 간세포 암으로 경동맥화학색전술을 시행한 105 명의 환자 중에 73 명에서 불완전한 색전술이 시행되었다. 그 중에 35 명의 환자는 경동맥화학색전술을 반복적으로 시행하였고 (TACE 군) 나머지 38 명은 방사선치료를 시행하였다 (TACERT 군). 모든 환자는 UICC 병기 III, IVa 였고, 간외전이가 없고 ECOG 2 이하이며, Child-Pugh class B 이하였다. 환자특성에서 두 군간의 유의한 차이는 없었다. 방사선치료 전에 시행된 경동맥화학색전술의 횟수는 평균 2 회 (1-5)였고 7-10 일 후에 방사선 치료가 시행되었으며 조사선량은 중앙값은 54 Gy 였다.

결 과: 2 년 생존율은 TACE 군 보다 TACERT 군에서 유의있게 높았다 (36.8% 대 14.3%, p=0.001). 종양의 크기에 따라 분석해 본 결과 TACERT 군과 TACE 군의 2 년 생존율은 5-7 cm 에서 63%, 42% (p=0.22); 8-10 cm 에서 50%, 0% (p=0.03); >10 cm 에서 17%, 0% (p=0.0002)였다. 급 만성/만성 독성은 TACERT 군에서 등급 3 의 간 독성이 13.2%, 등급 2 의 위장관 독성이 13.2% 에서 나타났으나 사망에 관련된 독성은 없었다.

결 론: 절제 불가능한 간세포 암에서 경동맥화학색전술 후 방사선치료를 추가하였을 때 생존율이 의미 있게 향상되었으며, 특히 크기가 8 cm 이상에서 효과가 있는 것으로 나타났다. 따라서 절제 불가능한 간세포 암에서 경동맥화학색전술 후 추가적인 방사선치료는 강력히 추천할만한 치료방법이라고 생각된다.

핵심 되는 말: 간세포 암, 화학 색전술, 방사선치료