Original Article

The retrospective cohort study for survival rate in patients with advanced hepatocellular carcinoma receiving radiotherapy or palliative care

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Background/Aims: This study was conducted to investigate the assessment of treatment efficacy of radiotherapy (RT) and other therapeutic modalities compared with palliative care only for treatment with advanced hepatocellular carcinoma (HCC). **Methods:** From 2002 to 2010, based on the case of 47 patients with advanced HCC, we have investigated each patients' Child-Pugh's class, ECOG performance, serum level of alpha fetoprotein and other baseline characteristics that is considered to be predictive variables and values for prognosis of HCC. Out of overall patients, the 29 patients who had received RT were selected for one group and the 18 patients who had received only palliative care were classified for the other. The analysis in survival between the two groups was done to investigate the efficacy of RT. **Results:** Under the analysis in survival, the mean survival time of total patients group was revealed between 30.1 months and 45.9 months in RT group, while it was 4.8 months in palliative care group, respectively. In the univariate analysis for overall patients, there were significant factors which affected survival rate like as follows: ECOG performance, Child-Pugh's class, the tumor size, the type of tumor, alpha fetoprotein, transarterial chemoembolization, and RT. The regressive analysis in multivariate Cox for total patients. No treatment under radiotherapy and high level of Child-Pugh's class grade were independent predictors of worse overall survival rate in patients. In contrast, for the subset analysis of the twenty-nine patients treated with radiotherapy, the higher serum level of alpha fetoprotein was an independent predictors of worse overall survival rate in patients. **Conclusions:** We found that the survival of patients with advanced HCC was better with radiotherapy than with palliative care. Therefore, radiotherapy could be a good option for in patients with advanced HCC. **(Korean J Hepatol 2011;17:189-198)**

Keywords: Hepatocellular carcinoma; Radiotherapy; Survival rate; Alpha-fetoprotein; Child-Pugh class

INTRODUCTION

Pursuant to the the data of National Statistical Information Service of the Ministry for Health, Welfare and Family Affairs in 2009, hepatocellular carcinoma (HCC) is ranked the fourth in the incidence rate of cancer like as follws : gastric cancer, colorectal cancer and lung cancer. In addition, the annual report of Statistics Korea on death causes in 2008 showed that HCC recorded the second highest mortality rate, showing 16.4% of the total death caused by cancer only after lung cancer.[1] Because it showed relatively advanced stages at diagnosis in a variety of cases, radical hepatic resection was available only in limited cases and liver cirrhosis as a underlying disease which occurred in many cases along with multiplicity.[2,3]

As radiotherapeutic technology has currently progressed, radiotherapy has been conducted continuously in order to

prevent the recurrence and to increase the survival rate after nonsurgical treatments of advanced HCC.[4] Radiotherapy is applied to HCC patients who cannot be treated with surgical resection or with a radical treatment such as a locoregional treatment and transarterial chemoembolization (TACE). It is mainly executed for patients with liver function of A or upper B in Child-Pugh's classification, and its response rate and median survival time were reported to be 40-90% and 10-25 months, respectively.[4] The indication of radiotherapy for safe treatment, which provokes only a few side effects, is that the volume of the tumor is less than one third of the total liver volume.[5] Furthermore, the indications of extended radiotherapy show that it is less than two thirds or 70% of the total liver volume[6,7] and that the volume irradiated with 30 Gy is less than 60% of the total liver volume in dose-volume analysis.[8] Providing a high-dose irradiation as a local irradiation, not the whole liver irradiation, has been identified, which has been continuously reported that the combination therapy of radiotherapy and chemotherapy or TACE for HCC works favorably.[9-11] What is more, in case of the patients who are not under other treatments or associating with portal vein thrombosis,[12-15] radiotherapy was safe and effective to raise the survival rate.[16] The radiotherapy had the effect of relieving cancer pain, improving symptoms through the decrease of lesions, lengthening the survival time in the circumstances with the biliary obstruction of a tumor associated with jaundice,[17,18] and extending the survival time in patients with abdominal lymph node metastasis.[19] However, even now it is not uncommon that only best palliative care can be maintained when it is hard to treat advanced HCC actively or when the general condition of a HCC patient is not appropriate. As a result, this study is focused on analyzing whether radiotherapy leads to a significant difference in the survival rate, comparing not only advanced HCC patients who have underwent treatments based on radiotherapy but also with those who have received only conservative ones.

PATIENTS AND METHODS

Patients

The critical point of this retrospective research was the medical record of overall 47 patients under advanced HCC of Barcelona Clinic Liver Cancer (BCLC) stage C or D diagnosed at Chungnam National University Hospital from January 2002 to March 2010.[20] The patients who recorded C in Child-Pugh's classification or with a diffuse tumor were excluded.[21] Diagnosis

criteria of HCC were hepatic nodules which were confirmed through liver ultrasonography and others, alpha fetoprotein (AFP) of over 200 ng/mL and findings which were appropriate to HCC in one of the contrast-enhanced dynamic computerized tomography (CT) and contrast-enhanced dynamic magnetic resonance image (MRI). When AFP was less than 200 ng/mL, the patients were diagnosed as HCC, who showed appropriate features to HCC in two or three out of three imaging studies of the contrast-enhanced dynamic CT, the contrast-enhanced dynamic MRI and the hepatic angiography. Those results were based on the criteria which were provided by "Practice guideline for management of HCC 2009" jointly under the definition of the Korean Liver Cancer Study Group and National Cancer Center.[22] Out of the 47 patients, 29 were selected by excluding patients with distant metastasis. They completed their scheduled radiotherapy for one or more lesions among primary HCC, local lymph node metastasis and portal vein thrombosis sites without early discontinuance or delay from December 2005 to September 2009. Except for them, the other 18 received only palliative care. Under the definition of WHO, palliative care means the cases of receiving only passive treatments to improve the survival rate after the diagnosis of HCC.[23] It enables patients to improve the quality of life, assisting them from physical, mental and spiritual aspects until they face death, which leads them to accept the death as a normal process with reducing distress and pain rather than lengthening their life artificially.

The clinical and biochemical data of patients at diagnosis were investigated, which included the existence of ascites and hepatic encephalopathy and Child-Pugh's classification based on albumin, prothrombin time and total bilirubin. Others were also examined as followings: AFP, hepatitis B, hepatitis C, Eastern Cooperative Oncology Group (ECOG) score,[24] body mass index (BMI), and the history of smoking and drinking. According to the causes of liver cirrhosis, patients were classified into alcoholic, hepatitis B- and hepatitis C- related and idiopathic one. Liver cirrhosis was diagnosed by synthesizing the degree of decompensated features of the former liver, such as ascites, hepatic encephalopathy, jaundice and upper gastrointestinal bleeding, the results of clinical and clinicopathological examinations and medical references which were suggested as portal hypertension on endoscopy. As shown in Table 1, the characteristics of the total subjects are summarized significantly in the pattern of classification.

Table 1. Patients' characteristics

Characteristics	Total patients (n=47)	Radiotherapy (n=29)	Palliative care (n=18)	P-value
Age (years, mean±S.D.)	63.3±9.4	62.2±9.2	64.9±9.7	0.353
<60, n (%)	15	11 (73.3%)	4 (26.7%)	0.343
≥60, n (%)	32	18 (56.2%)	14 (43.8%)	
Gender				0.473
Male, n (%)	37	24 (64.9%)	13 (35.1%)	
Female, n (%)	10	5 (50.0%)	5 (50.0%)	
ECOG performance				0.009
1	40	28 (70.0%)	12 (30.0%)	
2	7	1 (14.3%)	6 (85.7%)	
Alcohol drinking				0.130
Yes	28	20 (71.4%)	8 (28.6%)	
No	19	9 (47.4%)	10 (52.6%)	
Smoking (packyears) mean±S.D.	14.7±17.1	16.6±18.3	11.8±14.8	0.357
BMI (kg/m^2) mean±S.D.	23.5±3.1	24.3±3.1	22.3±2.8	0.033
HBsAg				0.763
Positive	28	18 (64.3%)	10 (35.7%)	
Negative	19	11 (57.9%)	8 (42.1%)	
Anti-HCV				0.025
Positive	6	1 (16.7%)	5 (83.3%)	
Negative	41	28 (68.3%)	13 (31.7%)	
Liver cirrhosis	37	21 (56.8%)	16 (43.2%)	0.277
Etiology of cirrhosis				0.088
HBV	25	16 (64.0%)	9 (36.0%)	
HCV	4	0 (0%)	4 (100.0%)	
Alcoholic	6	4 (66.7%)	2 (33.3%)	
Idiopathic	2	1 (50.0%)	1 (50.0%)	
Child-Pugh's class				0.010
A	34	25 (73.5%)	9 (26.5%)	
B	13	4 (30.8%)	9 (69.2%)	

Data represents patients number (%). Pearson's chi-squared test, the independent two-sample t-test, or Fisher's exact test were used for statistical analysis.

SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; HBsAg, hepatitis B viral antigen; Anti-HCV, anti-hepatitis C viral antibody; HBV, hepatitis B virus; HCV, hepatitis C virus.

Types of HCC

In order to identify the most important variables on this research, the types of HCC were divided into massive, multino-dular, and single nodular ones by following the classification of Yuki et al[21] Regardless of the existence of a satellite nodule, the massive type can be defined into a large single mass.

Multinodular and single nodular ones consist of two or more separated nodules and single nodule, respectively. In addition, HCC was analyzed into classifying under the size of the tumor and the existence of portal vein thrombosis. The size of the tumor was measured on CT image, which was done for single nodular HCC with the longest diameter of the nodules and for

Table 2. Tumor characteristics and treatments

Characteristics	Total patients (n=47)	Radio-therapy (n=29)	Palliative care (n=18)	P-value
Tumor type				0.215
Massive	8	3 (37.5%)	5 (62.5%)	
Multinodular	26	16 (61.5%)	10 (38.5%)	
Single nodular	13	10 (76.9%)	3 (23.1%)	
The number of tumor				0.365
<5	28	19 (67.9%)	9 (32.1%)	
≥5	19	10 (52.6%)	9 (47.4%)	
The size of tumors (cm)				<0.001
<5	23	20 (87.0%)	3 (13.0%)	
≥5	24	9 (37.5%)	15 (62.5%)	
Okuda stage				<0.001
1	28	23 (82.1%)	5 (17.9%)	
2	12	3 (25.0%)	9 (75.0%)	
3	7	3 (42.9%)	4 (57.1%)	
BCLC stage				0.003
C	39	28 (71.8%)	11 (28.2%)	
D	8	1 (12.5%)	7 (87.5%)	
AFP (ng/mL)				
Mean	7669.2±28 046.3	3221.1±9128.4	10731.6±32 880.8	0.759
<200	30	20 (66.7%)	10 (33.3%)	0.533
≥200	17	9 (52.9%)	8 (47.1%)	
Lymph node				0.739
Yes	13	9 (69.2%)	4 (30.8%)	
No	34	20 (58.8%)	14 (41.2%)	
Potal vein thrombosis				1.000
Yes	28	17 (60.7%)	11 (39.3%)	
No	19	12 (63.2%)	7 (36.8%)	
TACE				<0.001
Yes	25	25 (100.0%)	0 (0%)	
No	22	4 (18.2%)	18 (81.8%)	
Chemo-therapy				0.069
Yes	6	6 (100.0%)	0 (0%)	
No	41	23 (56.1%)	18 (43.9%)	
Operation				0.018
Yes	9	9 (100.0%)	0 (0%)	
No	38	20 (52.6%)	18 (47.4%)	

Data represents patients number (%). Pearson's chi-squared test or Mann-Whitney U-test were used for statistical analysis. BCLC, Barcelona Clinic Liver Cancer; AFP, alpha fetoprotein; TACE, transarterial chemoembolization.

multinodular one with the sum of the two longest diameter of the nodules. Each size was classified into two groups of less than 5 cm and 5 or more than 5 cm. Meanwhile, portal vein thrombosis was examined through CT or hepatic arteriography. The detailed HCC which is related to morphologic classification, stages and portal vein invasion of the subjects are presented in Table 2.

Treatments of HCC

While clinical trials are under way for this study, 29 patients have underwent radiotherapy for HCC, including both of patients

who have received only radiotherapy and those with TACE, hepatic resection, chemotherapy or combination therapy. Out of the 29 patients, 24 were treated only with radiotherapy during the treatment, while the others were done with radiotherapy and chemotherapy. 28 patients received other treatments before radiotherapy, and 17 got an additional treatment after it. For TACE, according to priority of treatment procedures, a catheter was inserted to the hepatic artery through arteriopuncture of the inguinal area, the combination of 10 ml lipiodol and 50 mg doxorubicin as antitumor agents was injected into the hepatic artery selectively, and then gelfoam was injected lastly.

The dose for radiotherapy was not only determined by individualizing patients under their general conditions and stages, but they were also irradiated by using a 10 megavolt (MV) linear accelerator. The patients under the radiotherapy were irradiated with daily dose of 2Gy for five days per week. Overall exposure dose was 45.9±10.6Gy in average, and 3D conformal radiotherapy was utilized for the irradiation. The radiotherapy was performed for one patient as initial treatment and for the other 28 ones as rescue therapy.

Evaluation of response to treatment

Response to the treatment was evaluated through CT for a follow-up in 6-8 weeks after the radiotherapy. There were four significant cases associated with the size of tumor and portal vein thrombosis. The definitions for each case are followed: Complete response (CR) was tabulated without any tumor and portal vein thrombosis. Partial response (PR) was measured into the decrease in the longest diameter of the largest nodule or the sum of the longest diameter of the largest two nodules by over 50%. No response (NR) was defined into the decrease by less than 50% or no change and the increase in the number of lumps. Progressive disease (PD) was classified as the increase in the size of a tumor by over 25%.[25,26] The responder group was the addition of CR and PR groups and the non-responder group was that of NR and PD groups.[25]

Statistical analysis

The frequency and proportion of patients receiving each treatment modality were calculated and tabulated with SPSS version 13 (SPSS Inc.)® for statistical analysis. The results were presented with mean value and standard deviation, and, if necessary, percent (%) was used with each individual number. Overall survival time was defined as the period from the diagnosis date to the death of date for patients expired, and from the diagnosis date to the date of the last follow-up for surviving patients. To compare basic characteristics of the radiotherapy and the palliative care groups, Pearson's chi-squared test and independent two-sample *t*-test were performed. When the cases with an expected frequency of less than 5 was over 25% of the contingency table, Fisher's exact test was applied. As the variation of AFP was severer in standard deviation compared to its mean value, Mann-Whitney *U*-test or a non-parametric test was used. The survival rate was analyzed with Kaplan-Meier method, and a log-rank test was conducted to compare and analyze the survival curve by each factor. To exclude the correlation among factors which influence the survival rate significantly, multivariate analysis was performed with Cox regression analysis, using Cox's proportional hazard model. A *P*-value of <0.05 was considered to be significant statistically.

RESULTS

Clinical and clinicopathological characteristics

The number of all the patients registered for this study was totally 47, who were 37 males and 10 females under the average of 63.3±9.4 years old. At the time of diagnosis on HCC, 37 (78.7%) patients had liver cirrhosis. Out of the liver cirrhosis patients, 24 (64.9%) and 13 (35.1%) were recorded as A and B in Child-Pugh's classification, respectively.

As shown in Table 1, BMI was not different significantly between the radiotherapy and the conservative treatment groups by recording 24.3±3.1 kg/m² and 22.3±2.8 kg/m², respectively. As for morphological characteristics of tumors, massive, multinodular and single nodular types were found in 8 (17.0%), 26 (55.3%) and 13 (27.7%) patients each. The mean AFP was 7669.2±28 046.3 ng/mL (1.5-175,000 ng/mL). While AFP of 12 patients was within the normal range (<10 ng/mL), AFP of 18 patients was over 200 ng/mL (Table 2).

Comparison of characteristics between the radiotherapy and the palliative care groups, and response to radiotherapy

When the 29 patients undergoing radiotherapy were compared and analyzed with the 18 receiving only palliative care, the rate of patients who recorded two points in ECOG performance status was significantly higher (*P*=0.009), the rate of hepatitis C patients was also higher (*P*=0.025) and the grade in Child-Pugh's

classification was higher (*P*=0.010), in the palliative care group than in the radiotherapy group. In addition, patients with a large tumor were observed more frequently in the palliative care group (*P*<0.001) and both of Okuda and BCLC stages were advanced in the palliative care group (*P*<0.001, *P*=0.003). Except for them, as shown in Table 1 and 2, the other factors did not have any significant differences statistically between the two groups. The radiotherapy group was divided into the responder group under CR (n=4, 13.8%) and PR (n=7, 24.1%) and the non-responder group under NR (n=8, 27.6%) and PD (n=10, 34.5%), including 11 (37.9%) and 18 (62.1%) out of the 29 patients, respectively.

Survival analysis

The follow-up period for overall patients to be observed was 25.0 (1-110) months in average. The mean survival time of the total patients was 30.1 (19.8-40.4) months, and that of the radiotherapy and the palliative care groups recorded 45.9 (32.0-59.8) and 4.8 (2.0-7.6) months, respectively (*P*<0.001).

Univariate analysis of all the subjects revealed that the group recording two points of ECOG performance status showed much shorter survival period than that with one point and the difference was significant statistically (8.0 vs. 34.0) (*P*=0.005). As the mean survival time of the groups with Child-Pugh's classification A and B was respectively 38.4 and 9.8 months, higher grade was significantly associated with shorter survival time (*P*<0.001). The mean survival time of the groups with the size of a tumor nodule of less than 5 cm and over 5 cm was 46.6 and 11.5 months each, so the group with a larger nodule had shorter survival time (*P*<0.001). In addition, the mean survival time of the massive type and the multinodular type was reduced significantly, comparing to that of the single nodular type (7.5 vs. 33.1 vs. 42.0 months) (*P*=0.010). The group with AFP of over 200 ng/mL had significantly shorter survival time than that with AFP of less than 200 ng/mL (12.8 vs. 37.5 months) (*P*=0.023). For the other factors except for them, there was no significant difference in the survival time (Table 3).

After dividing the radiotherapy and the palliative care groups

Table 3. Univariate analysis of overall survival of all patients (n=47)

	Variable	N	Mean survival (months)	*P*-value
Age (years)	<60/≥60	15/32	31.2/30.2	0.938
Sex	M/F	37/10	30.3/29.0	0.978
BMI	≤23.0/>23.0	18/29	31.4/30.9	0.979
ECOG	1/2	40/7	34.0/8.0	0.005
Child-Pugh's class	A/B	34/13	38.4/9.8	<0.001
The number of tumor	<5/≥5	28/19	24.3/40.5	0.265
Tumor size (cm)	<5/≥5	23/24	46.6/11.5	<0.001
Type of tumor	Massive/multi-nodular/single nodular	8/26/13	7.5/33.1/42.0	0.010
AFP (ng/mL)	<200/≥200	30/17	37.5/12.8	0.023
Portal vein thrombosis	Yes/No	28/19	23.0/40.7	0.101
Radiotherapy	Yes/No	29/18	45.9/4.8	<0.001
TACE	Yes/No	25/22	48.1/10.0	<0.001
Alcohol drinking	Yes/No	28/19	27.5/34.5	0.788
HBsAg	Yes/No	28/19	33.4/24.9	0.664
Anti-HCV	Yes/No	6/41	15.8/31.5	0.395
Liver cirrhosis	Yes/No	37/10	28.2/33.4	0.415
Operation	Yes/No	9/38	46.8/26.2	0.107
Chemotherapy	Yes/No	6/41	42.2/27.9	0.224

Kaplan-Meier method or log-rank test were used for statistical analysis.
BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; AFP, alpha fetoprotein; TACE, transarterial chemoembolization; HBsAg, hepatitis B viral antigen; Anti-HCV, anti-hepatitis C viral antibody.

into Child-Pugh's classification A and B groups, respectively (RT-A, RT-B, palliative care-A and palliative care-B) the survival analysis was conducted. The mean survival time of RT-A, RT-B, palliative care-A and palliative care-B groups was 49.7, 26.5, 7.3 and 2.3 months, respectively (*P*<0.001) (Fig. 1).

According to multiple regression analysis through Cox regression model with the total subjects, the outcome in Table 4 shows that patients recording a lower grade in Child-Pugh's classification and undergoing radiotherapy showed significantly longer survival time even after adjusting significant factors which were observed in univariate analysis.
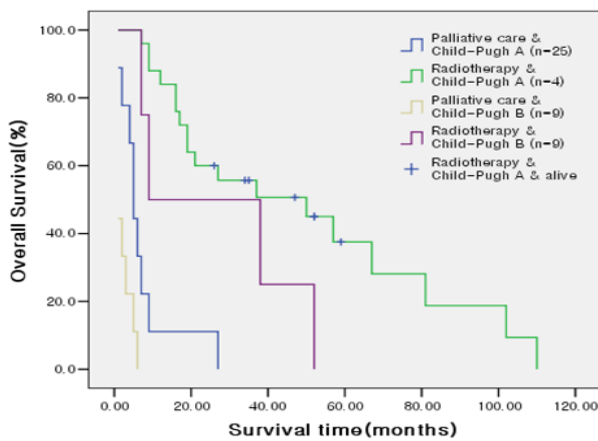

Figure 1. Comparison of overall survival of patients with advanced hepatocellular carcinoma treated with radiotherapy or palliative care based on Child-Pugh classes A and B (Kaplan-Meier method, log-rank test, *P*<0.001).

As shown in Table 5, the partial analysis for 29 patients undergoing radiotherapy by univariate analysis showed that the higher an AFP level was, the shorter survival time was significantly (*P*=0.039). Likewise univariate analysis, multiple regression analysis which was conducted only for the radiotherapy group also revealed that the group with AFP of over 200 ng/mL had shorter survival time significantly, as shown in Table 6.

DISCUSSION

This is a retrospective study which analyzed the survival rate by comparing the groups undergoing radiotherapy and only palliative care with HCC patients. As mentioned before, the total subjects of this study had HCC on the advanced stages, and the radiotherapy group received various treatments before and after radiotherapy.

For most patients with advanced HCC, it is difficult to treat them actively due to their poor general conditions or performance status. If radical treatment is performed for these patients excessively, the risk of death following hepatic failure can increase easily. That's the reason why non-radical treatments are applied. In the radiotherapy group, most patients underwent radiotherapy as rescue therapy (28 out of 29, 96.6%). Because of it, the response rate of this study or 37.9% was slightly lower than that observed overall in previous studies applying the irradiation of a similar dose or 40-60%.[4,12,27]

Table 4. Multivariate analysis of overall survival of all patients (n=47)

Variables	Wald	Hazard ratio (95% confidence interval)	*P*-value
Gender (female vs. male)	1.03	1.74 (0.60-5.03)	0.310
Age (<60 vs. ≥60)	0.02	1.07 (0.46-2.49)	0.879
ECOG (1 vs. 2)	0.27	0.76 (0.27-2.15)	0.602
AFP (ng/mL) (<200/≥200)	2.55	2.00 (0.86-4.52)	0.110
TACE (No vs. Yes)	0.81	0.55 (0.15-2.01)	0.367
Radiotherapy (No vs. Yes)	7.40	0.12 (0.03-0.55)	0.007
Tumor size (cm)	0.78	1.65 (0.54-5.02)	0.378
Type of tumor	1.04		0.600
Single nodular vs. massive	0.46	1.62 (0.40-6.47)	0.499
Single nodular vs. multinodular	0.01	0.95 (0.34-2.66)	0.922
Child-Pugh's class (A vs. B)	5.58	3.15 (1.22-8.18)	0.018

Cox regression analysis was used for statistical analysis.
ECOG, Eastern Cooperative Oncology Group; AFP, alpha fetoprotein; PVT, portal vein thrombosis; TACE, transarterial chemoembolization.

Table 5. Univariate analysis of overall survival of the subset analysis of the 29 patients treated with radiotherapy (n=29)

	Variable	N	Mean survival (months)	P-value
AFP (ng/mL)	<200/≥200	20/9	53.4/21.2	0.039
Alcohol drinking	Yes/No	20/9	36.9/66.6	0.088
RT target	Main-mass/PVT/LN/Main mass+PVT+LN	11/12/5/1	68.4/29.8/26.8/67	0.064
RT response	CR/PR/NR/PD	4/7/8/10	49.0/57.3/28.8/42.4	0.236
RT response category	Responder/non-responder	11/18	61.9/36.6	0.064

Kaplan-Meier method or log-rank test were used for statistical analysis.
AFP, alpha fetoprotein; PVT, portal vein thrombosis; LN, lymph node; CR, complete response; PR, partial response; NR, no response; PD, progressive disease; RT, radiotherapy.

Table 6. Multivariate analysis for overall survival for the subset analysis of the 29 patients treated with radiotherapy (n=29)

Variables	Wald	Hazard ratio (95% confidence interval)	P-value
Gender (female vs. male)	0.12	1.26 (0.34-4.75)	0.730
Age (<60 vs. ≥60)	1.49	0.54 (0.20-1.46)	0.222
AFP (ng/mL) (<200/≥200)	4.96	3.30 (1.15-9.42)	0.026

Cox regression analysis was used for statistical analysis.
AFP, alpha fetoprotein.

Because radiotherapy for HCC utilized the irradiation to the whole liver in the past, there were many limitations in determining a therapeutic dose due to hepatic failure and side effects of irradiation of over a certain dose. However, it was found that high-dose irradiation to a localized part of the liver did not provoke hepatotoxicity,[17,28,29] and that the therapeutic dose could be raised by deciding the range for the therapy selectively. In particular, for 3D conformal radiotherapy which was provided for most patients in this study, it is well known that it improves the survival rate of patients with advanced HCC associated with embolism by increasing its therapeutic effect, declining side effects and reaching the target radiation dose effectively compared to conventional radiotherapy.[11,13,25]

Meanwhile, the combination of TACE and local radiotherapy has been applied continuously to primary HCC which cannot be resected, and its positive outcomes of enhancing the survival rate have been reported.[12,30] In particular, antitumor agents, which were used during TACE to tumor cells on the tumor margin, work as radiosensitizers not only to increase the effect of radiotherapy but also to make TACE available by improving portal vein thrombosis.[4] In this study, 26 patients out of total 29 ones in the radiotherapy group (89.7%) underwent TACE before and after radiotherapy, which was considered to affect their survival rate significantly. As the mechanism was mentioned, multivariate analysis including both of TACE and radiotherapy

was conducted. However, TACE did not produce any significant effect on the improvement of the survival rate in the patients who were selected on this study.

Although basic characteristics of the two groups were largely different in this study, it was only a limitation of a retrospective study reviewing the medical record, and the result was considered to be unavoidable except for a well-designed prospective study. Death causes in most cases were hepatic failure, upper gastrointestinal bleeding and hemorrhage caused by ruptured tumor following hepatic metastasis of HCC, portal vein thrombosis and secondary portal hypertension. Like this, whether radiotherapy for much advanced HCC patients is helpful in boosting the survival rate could be clinically controversial, this study was conducted based on the assumption. Multivariate regression analysis with the total subjects found that lower grade in Child-Pugh's classification or a representative factor as an index of liver function and general condition before treatment was associated significantly with longer survival time and radiotherapy increased the survival time as well. Multivariate regression analysis, as partial analysis with the 29 patients undergoing radiotherapy, revealed that higher AFP was a prognostic factor related to the decrease of the survival rate. The finding was the same as that of previous studies reporting that increased AFP would be associated with poor prognosis.[31-33] When the results of multivariate analysis of the two groups were

put together, the survival rate of advanced HCC were associated with all internal and external factors related to treatments for HCC such as the general condition of a patient (Child-Pugh's classification), the progression and the burden of a tumor (AFP) and radiotherapy. This finding strongly suggests that radiotherapy as rescue therapy for portal vein thrombosis or primary lump and regional nodal metastasis as well as efforts to improve the general condition should be provided to increase the survival rate of HCC patients.

As a retrospective study reviewing such medical records as this study has a possibility of selection bias, it should be considered in interpreting its results. This study divided the subjects into two groups receiving various treatments along with radiotherapy and doing palliative care by considering its purpose, but basic characteristics of the two groups were largely different. In addition, this study did not consider complications due to toxicity of treatments such as radiotherapy induced liver disease (RILD) because it was hard to determine which one increased liver enzyme levels in the advanced HCC patients between radiotherapy and the disease itself. Moreover, analysis on improving the quality of life of in investigating detailed symptoms and clinical outcomes of patients after radiotherapy, is thought to be necessary.

In conclusion, if radiotherapy is available for HCC patients by synthesizing their general condition and tumor-related factors, an appropriate radiotherapy is expected to increase the survival rate. In particular, based on the results of this study when there was no distant metastasis that the type is not diffuse, AFP is less than 200 ng/mL, and the grade of Child-Pugh's classification is A or B in advanced HCC patients, radiotherapy should be considered actively as its effect so as to improve the survival rate is higher in the cases.

Prospective studies, analyzing the usefulness of radiotherapy to boost the survival rate by comparing patients with similar clinical characteristics who were treated with radiotherapy and not done, are more necessary in the future. Furthermore, as the outcomes of tomotherapy as well as of the previous 3D conformal radiotherapy have been reported continuously, prospective studies applying them and analyzing the treatment group and the non-treatment group, are expected.

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