

2004 12



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가

가

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가

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	1
I.	3
II.	7
III.	11
1.	11
2.	13
가. JIS score.....		13
.	14
.	15
.	15
3.	15
4. 5	21
IV.	24
V.	30
	31
Abstract		37

Fig. 1. Cumulative survival curve of 470 patients with HCC
treated by TACE (Kaplan - Meier method) 12

Fig. 2. Cumulative survival curves according to JIS score,
tumor necrosis rate (TNR) and tumor type 21

Table 1. Modified UICC TNM stage by Liver Cancer Study Group of Japan	5
Table 2. Japan Integrated Staging (JIS) scoring system	5
Table 3. Univariate analysis of prognostic factors associated with patient ' s characteristics	12
Table 4. Univariate analysis of JIS scoring system.....	13
Table 5. Univariate analysis of prognostic factors associated with TACE.....	14
Table 6. Univariate analysis of prognostic factors associated with tumor state.....	16
Table 7. Univariate analysis of prognostic factors associated with liver function.....	17
Table 8. Multivariate analysis except Child - Pugh classification, TNM stage, and JIS scoring system	18
Table 9. Multivariate analysis including JIS scoring system	20
Table 10. Comparison of the prognostic factors of the patients who survived 5years or more with those of the patients who survived less than 5years	22

가

.

,

, 5

Japan integrated staging(JIS) score

가

1997 1 1 2001 12 31

470

lipiodol adriamycin

gelfoam

Kaplan - Meier method

log -

rank test

Cox's proportional hazard model . 5

5

가

Student

t - test, ² - test, Fisher's exact test .

20.8 1, 2, 3, 4, 5
 66.1%, 45.0%, 34.1%, 28.2%, 22.0% .
 JIS score가 ,
 , microcatheter , ,
 ,
 , , , , , ,
 , TNM 가 ,
 ,
 prothrombin index, , Child - Pugh 가 .
 JIS score 가 가
 , , , , ,
 가 . 5
 5 가
 microcatheter
 가

JIS score가 ,
 가 .

: ; ; ;

< >

I.

, .

B ,

, 6
가 1,2,

2002 10 23.1

, 3

가

가 ,

가

가 3,4,

5.

(thermal ablation), (cryotherapy),

1983 Yamada 가 7

6 가

가

8-25 가

가가 26-30가 ,

가 ,

가 가

1,31,32

가

gelfoam 13,15,18-25

gelfoam

가

Kudo 33 modified UICC

TNM stage³⁴ (Table 1) Child - Pugh

Japan integrated staging(JIS) score

(Table 2). Child - Pugh A 0 , B 1 , C

2 TNM stage I 0 , II 1 , III 2 , IV 3

Child - Pugh TNM stage

JIS score 0~5 . Kudo

Table 1. Modified UICC TNM stage by Liver Cancer Study Group of Japan

Factors	I. Single	II. Size < 2cm	III. No vessel invasion
T1	Fulfilling three factors		
T2	Fulfilling two factors		
T3	Fulfilling one factor		
T4	Fulfilling 0 factors		
N0	Absence of lymph node metastasis		
N1	Presence of lymph node metastasis		
M0	Absence of extrahepatic metastasis		
M1	Presence of extrahepatic metastasis		
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
Stage IV - A	T4	N0	M0 or T1 - 4 N1 M0
Stage IV - B	T1 - 4	N0 - 1	M1

Table 2. Japan Integrated Staging (JIS) scoring system

Variables	Scores			
	0	1	2	3
Child - Pugh classification	A	B	C	
TNM stage by LCSGJ	I	II	III	IV

Summation of Child - Pugh score and TNM stage score is defined as JIS score (0~5).

LCSGJ, Liver Cancer Study Group of Japan

³³ 가 Cancer of the Liver Italian Program (CLIP)
score³⁵
(discrimination ability) (predictive
power) (stratification ability)
. C , B

JIS score , 가 ,
가 .
JIS score ,
score 가 . , 5 JIS

II.

1997 1 1 2001 12 31

470

1844

674

470

204

(96)

(61)

(37)

가

, CT, MRI,

2

가

2cm

가

, CT, MRI,

1가

2cm

400ng/mL

36

가

adriamycin

(20~70mg)

3cc

lipiodol(2~20cc)

pumping

, gelfoam

1mm

. Lipiodol
 20cc
 gelfoam .
 1~2 CT MRI
 , CT MRI
 , CT 1
 lipiodol .
 , JIS score 가
 ,
 microcatheter , ,
 ,
 , , , , , ,
 , TNM ,
 Child - Pugh , , ,
 prothrombin index, ,
 , .
 . (1)
 gelfoam adriamycin lipiodol
 gelfoam
 , (2)
 CT MRI 가 ,
 가 complete response (CR), 50%
 가 partial response (PR),

가 50% stable disease (SD) .
 (3) 가 1 (2)
 Egge (nodular type),
 (massive type), (diffuse type) .

34

가 50% 가 50%
 , 가 1
 2
 (multinodular type) . (4)

, (5)
 , (6) TNM modified
 UICC TNM stage³⁴ . (7) Child - Pugh

34

Child - Pugh
 가 5, 6 A, 7 - 9 B, 10 - 15
 C . (8) 3.5g/dL, (9)
 1.2mg/dL, (10) prothrombin index 50% .
 (11) 55 (12) B
 , C , B C , NBNC

가

,
 (censored data)
 .
 5 Kaplan -
 Meier method .
 log - rank test
 ,
 Cox's proportional hazard model
 p 0.05 .
 5 5
 가
 Student t - test, χ^2 - test, Fisher's exact test ,
 p 0.05
 .
 SPSS 12.0 for Windows (Release
 12.0.0) .

III.

470 19 85
 55 , 378 , 92

4.1:1 .

가 92 ,
 가 378 .

16 454 HBsAg
 가 357 (78.6%), anti-HCV 가 55 (12.1%),
 가 5 (1.1%), (NBNC)가
 37 (8.2%) . HBsAg HBeAg
 116 HBeAg 40.9% . ,
 , 가
 (Table 3).

1.

470 363
 , 107
 ,

가 5
 ,

112 (23.8%) .

20.8 , Kaplan - Meier
 method 1 , 2 , 3 , 4 , 5
 66.1%, 45.0%, 34.1%, 28.2%, 22.0% (Fig. 1).

Table 3. Univariate analysis of prognostic factors associated with patient's characteristics

Factor	No. of patients	Median survival (months)	p -value
All patients	470	20.8	
Age			
< 55	213	17.1	0.66
≥ 55	257	22.1	
Sex			
Male	378	19.8	0.27
Female	92	24.2	
Cause of Hepatitis			
Hepatitis B	357	17.0	>0.1 [†] in all combinations
Hepatitis C	55	26.5	
Hepatitis B&C	5	12.7	
NBNC	37	25.6	

† p -value is insignificant (> 0.05) in all the combinations of the causes of hepatitis (B - C, B - B&C, B - NBNC, C - B&C, C - NBNC, and B&C - NBNC).

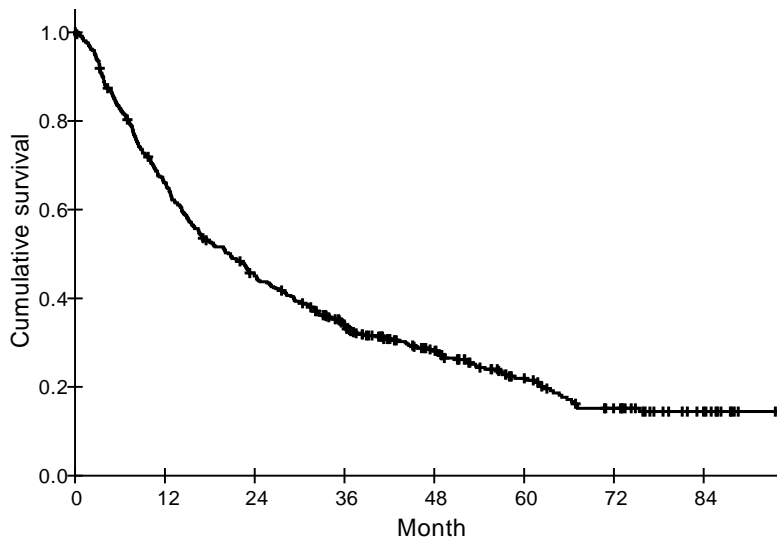


Fig. 1. Cumulative survival curve of 470 patients with HCC treated by TACE (Kaplan - Meier method)

2.

Log - rank test

가. JIS score

JIS score 0 6.8%, 1 29.4%, 2 37.9%, 3 21.1%, 4 4.3%, 5 0.6%

3 가

JIS score (Table 4).

Table 4. Univariate analysis of JIS scoring system

Factor	No. of patients	Median survival (month)	<i>p</i> - value
JIS score			
0	32	75.5	<0.0001 [†] in all combinations
1	138	36.1	
2	178	21.0	
3	99	8.5	
4	20	3.6	
5 [§]	3	-	

§ The group of JIS score 5 was excluded from the univariate analysis due to small number (n=3).

† *p* - value is very significantly low (<0.0001) in all the combinations of JIS scores (0 - 1, 0 - 2, 0 - 3, 0 - 4, 1 - 2, 1 - 3, 1 - 4, 2 - 3, 2 - 4, and 3 - 4).

1 - 8
 1 가 47.7%, 2
 52.3% . microcatheter
 70.0% , 35
 (7.4%) 15 가
 13 ,
 ,
 CT MRI
 436 complete response 42.7%, partial response
 47.5%, stable disease 9.7% .
 (Table 5).

Table 5. Univariate analysis of prognostic factors associated with TACE

Factors	No. of patients	Median survival (month)	<i>p</i> - value
Number of TACE			
1	224	11.3	<0.0001
2	246	30.0	
Microcatheter			
Used	329	23.2	0.012
Not used	141	15.2	
Collateral artery			
Absent	435	22.2	<0.0001
Present	35	7.2	
Tumor necrosis rate (TNR)			
Complete response (CR)	186	37.5	<0.0001 [†] in all combinations
Partial response (PR)	207	16.0	
Stable disease (SD)	43	7.8	

[†] *p*-value is very significantly low (<0.0001) in all the combinations of TNR (CR - PR, CR - SD, and PR - SD).

35.3%, 33.4%,
 26.1%, 5.1% . TNM stage I 8.7%, II가
 35.7%, III가 41.5%, IV가 14.0% . TNM
 가 46.4%, 2 가
 53.6% , 2cm 8.9%, 2~5cm 가
 28.9%, 5cm 62.1% ,
 11.7%, 가 5.7%
 . 410 가
 400ng/mL 가 44.6% .
 (Table 6).

Child - Pugh A가 77.7%, B가 17.0%, C가 5.3% , A
 365
 가 38 (8.1%) . Child - Pugh
 , prothrombin
 index, (Table 7).
 (hepatic encephalopathy) 4
 가 .

3.

Cox's
 proportional hazard model .
 , Child - Pugh , TNM , JIS score

Table 6. Univariate analysis of prognostic factors associated with tumor state

Factors	No. of patients	Median survival (month)	<i>p</i> - value
Tumor type			
Nodular (N)	166	44.6	<0.05 [†] in all combinations
Multinodular (MN)	157	24.3	
Massive (M)	123	8.1	
Diffuse (D)	24	7.7	
TNM stage			
1	41	65.7	<0.01 [‡] in all combinations
2	168	32.3	
3	195	17.0	
4	66	7.23	
Number of tumors			
Single	218	32.0	<0.0001
Multiple	252	15.47	
Tumor size			
< 2cm	42	65.7	<0.01 [§] in all combinations
2~5cm	136	35.8	
5cm	292	13.7	
Portal vein thrombosis			
Absent	415	23.9	<0.0001
Present	55	7.6	
Extrahepatic metastasis			
Absent	443	22.7	<0.0001
Present	27	8.1	
- fetoprotein (ng/mL)			
< 400	227	24.5	0.0002
400	183	13.7	

† *p* - value is significantly low (<0.05) in all the combinations of tumor type (N - MN, N - M, N - D, MN - M, MN - D, and M - D).

‡ *p* - value is significantly low (<0.01) in all the combinations of TNM stage (1 - 2, 1 - 3, 1 - 4, 2 - 3, 2 - 4, and 3 - 4).

§ *p* - value is significantly low (<0.01) in all the combinations of tumor size (< 2cm - 2~5cm, < 2cm - 5cm, and 2~5cm - 5cm).

Table 7. Univariate analysis of prognostic factors associated with liver function

Factors	No. of patients	Median survival (month)	<i>p</i> - value
Child - Pugh classification			
A	365	26.0	<0.05 [†] in all combinations
B	80	12.7	
C	25	7.8	
Serum albumin (g/dL)			
> 3.5	261	27.5	<0.0001
3.5	209	15.1	
Serum total bilirubin (mg/dL)			
< 1.2	323	24.7	<0.0001
1.2	147	13.3	
Prothrombin index (%)			
> 50	448	21.5	0.0216
50	22	12.4	
Ascites			
Absent	391	23.9	<0.0001
Present	79	10.1	

† *p* - value is significantly low (<0.05) in all the combinations of Child - Pugh classification (A - B, A - C, and B - C).

가
10가 (Table 8).
가 ($p < 0.05$)

Table 8. Multivariate analysis except Child - Pugh classification, TNM stage, and JIS scoring system

Factors	SE	Exp()	95% CI		ρ
			Lower	Upper	
Tumor type					<0.001
(reference: Nodular)					
Nodular		1.000			
Multinodular	- 0.139	0.251	0.870	0.532 1.423	0.579
Massive	0.603	0.222	1.828	1.183 2.826	0.007
Diffuse	0.327	0.387	1.386	0.649 2.961	0.399
Multiple tumors	0.433	0.200	1.542	1.042 2.280	0.030
Tumor size					0.018
(reference: <2cm)					
< 2cm		1.000			
2~5cm	0.590	0.272	1.805	1.058 3.078	0.030
5cm	0.775	0.290	2.171	1.230 3.832	0.007
Distant metastasis	0.759	0.242	2.135	1.327 3.434	0.002
- fetoprotein 400ng/mL	0.311	0.120	1.365	1.080 1.726	0.009
Ascites	0.383	0.171	1.466	1.049 2.050	0.025
Serum albumin 3.5g/dL	0.345	0.126	1.411	1.102 1.807	0.006
Serum total bilirubin					
1.2mg/dL	0.379	0.136	1.461	1.120 1.905	0.005
Number of TACE 2	- 0.367	0.121	0.693	0.546 0.879	0.002
TNR (reference: CR)					0.005
Complete response (CR)		1.000			
Partial response (PR)	0.292	0.145	1.339	1.009 1.779	0.043
Stable disease (SD)	0.806	0.242	2.238	1.393 3.596	0.001

, coefficient; SE, standard error; EXP(), odds ratio; CI, confidence interval; TNR, tumor necrosis rate

microcatheter

JIS score

Child - Pugh TNM , JIS score

TNM Child - Pugh

JIS score,

5가 가

(Table 9).

JIS score 0 1, 2, 3, 4

가 stable

disease complete response

가 , partial response Table 8

JIS score

($p=0.043$), Table 9

JIS score

($p=0.091$)

가 . 2 TACE

1

가 ,

가

400ng/mL 가

(odds ratio)

JIS score 가 가 , 가 1

가 4.7, 8.7, 15.8, 62.1 가

JIS score 가 가가

Table 9. Multivariate analysis including JIS scoring system

Factors	SE	Exp()	95% CI		p
			Lower	Upper	
JIS score (reference: 0)					<0.001
0		1.000			
1	0.856	0.356	2.353	1.170 4.731	0.016
2	1.430	0.375	4.180	2.005 8.711	<0.001
3	1.995	0.389	7.351	3.429 15.758	<0.001
4	3.137	0.506	23.046	8.556 62.075	<0.001
TNR (reference: CR)					0.003
Complete response (CR)			1.000		
Partial response (PR)	0.237	0.140	1.267	0.963 1.666	0.091
Stable disease (SD)	0.820	0.234	2.270	1.436 3.588	<0.001
Number of TACE 2	-0.366	0.118	0.693	0.550 0.874	0.002
Tumor type (reference: Nodular)					<0.001
Nodular			1.000		
Multinodular	-0.128	0.181	0.880	0.618 1.253	0.478
Massive	0.568	0.190	1.765	1.216 2.563	0.003
Diffuse	0.193	0.359	1.213	0.600 2.451	0.591
-fetoprotein 400ng/mL	0.261	0.119	1.299	1.028 1.640	0.028

, coefficient; SE, standard error; EXP(β), odds ratio; CI, confidence interval; TNR, tumor necrosis rate

. JIS score 가
 stable disease (=2.3),
 (=1.8), (=1.3)
 , TACE 가 0.69 2 TACE
 가 1 가
 . JIS score, ,

Fig. 2 .

4.5

470
 , 5
 343
 5
 77
 5
 가
 50
 5
 73.5
 17.1

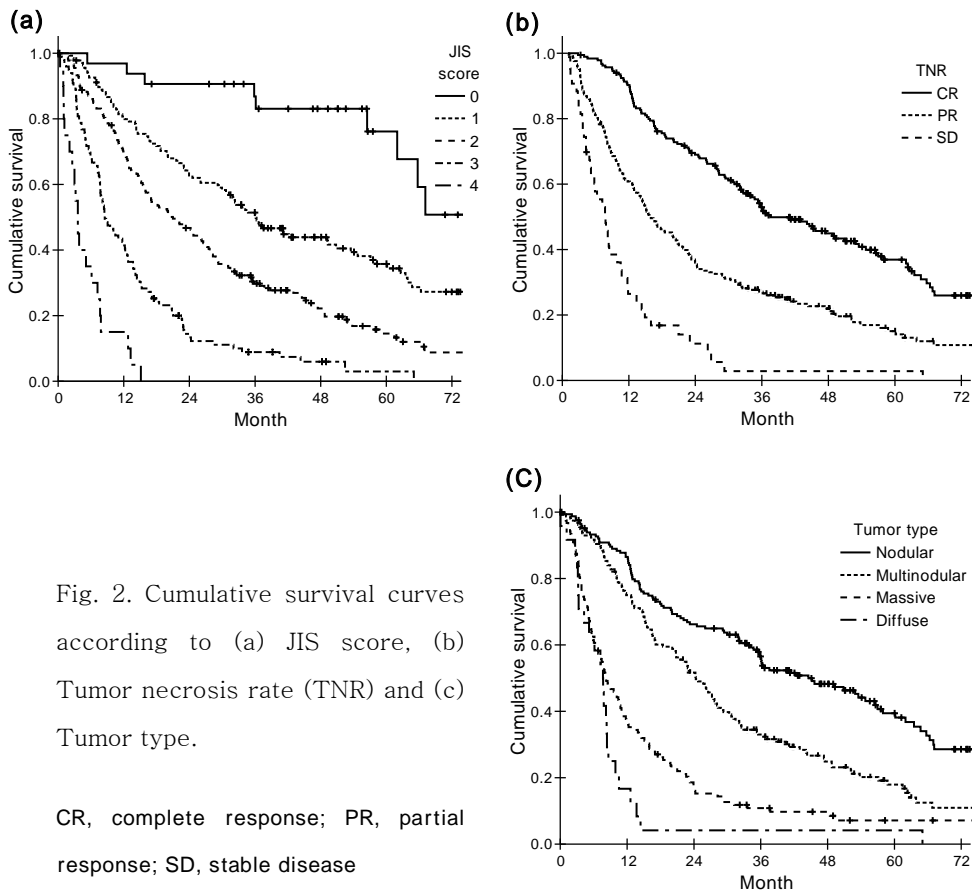


Fig. 2. Cumulative survival curves according to (a) JIS score, (b) Tumor necrosis rate (TNR) and (c) Tumor type.

CR, complete response; PR, partial response; SD, stable disease

Table 10. Comparison of the prognostic factors of the patients who survived 5years or more with those of the patients who survived less than 5years

	Survival period		ρ - value [†]
	5 years	< 5years	
Age (years)	53.4 ± 11.0	55.7 ± 10.8	0.175
Serum albumin (g/dL)	3.9 ± 0.5	3.5 ± 0.6	< 0.001
Serum total bilirubin (mg/dL)	0.86 ± 0.42	1.21 ± 0.96	< 0.001
Prothrombin index (%)	89.7 ± 12.7	85.1 ± 17.1	0.028
Number of TACE	2.5 ± 1.8	1.9 ± 1.2	0.035

† ρ - value was calculated by Student t - test

prothrombin index,

Student t - test

가 ($\rho < 0.05$) (Table 10).

microcatheter ² - test

JIS score, TNM, Child - Pugh,

Fisher's exact test

JIS score, TNM,

Child - Pugh,

(linear

by linear association) (likelihood ratio test

for trend) JIS score,

TNM, Child - Pugh,

가 가 가 가

. , , microcatheter .
 , 5 5
 가 Kaplan -
 Meier method log - rank test
 , microcatheter
 가 15가

IV.

lipiodol

³⁷,

lipiodol

gelfoam

가

doxorubicin, mitomycin

³⁸.

1983 Yamada ⁶

가

가 ⁷

가

1~2mm

gelfoam

가

(6), gelfoam

,

가 ^{39,40}, gelfoam

⁴¹. 1980

lipiodol

가

gelfoam

lipiodol - gelfoam

⁴².

8,10 -

12,14

1995

, lipiodol,

gelfoam

. Shijo ¹⁰

150

1, 3, 5

85.1%, 51.4%, 36.4%

가

. Yamamoto ¹¹

가

240

1, 2, 3

67.5%,

32.0%, 20.5%

가

. Hsieh ¹⁴

100

1, 2, 3

57%, 31%, 21%

, HBsAg, Child - Pugh ,

, 5cm

가

가

1996

, lipiodol, gelfoam

lipiodol

^{19 - 25}

gelfoam

^{20,24,25}

gelfoam

가

^{24,25}, gelfoam

가

가 ²⁰.

, Yamashita ⁹

275

, lipiodol, gelfoam

가 1, 2 62.3%, 43.8%

lipiodol 1, 2 37.8%, 18.3%

가 ,

Hatanaka ¹³ 가 322

, lipiodol, gelfoam

1, 3, 5 86.3%, 34.8%, 26.1% lipiodol

1, 3, 5 65.9%, 36.2%, 18.1%

, , , .

, lipiodol, gelfoam

470

1, 2, 3, 4, 5 66.1%, 45.0%,

34.1%, 28.2%, 22.0%

Yamamoto ¹¹ , Hatanaka ¹³

, lipiodol, gelfoam

, gelfoam

가

gelfoam .

17

. ,

, , TNM stage

,

Child - Pugh

TNM stage, Child - Pugh

.

8,9,11 - 14,19,20,22,23 ,

8,9,11,14,20,22,23 .

가

가

8,18,19,22,23,43 ,

18 .

5

5

가

,

가 1.34

가

가

가 2

가 1

21,24,25 , 4

가 3

20 ,

가

20,21 ,

2

1

CT MRI

가

partial response

complete response

1.3 , stable disease

complete response

2.2

가 (Table 8).

가
14, 가 CT lipiodol
16,24. Microcatheter
가
microcatheter 가
,
24,
5 5
microcatheter
가
가
,
microcatheter
, lipiodol gelfoam
가 , 가

가

gelfoam

44,45

가

JIS scoring system

modified

UICC TNM

Child - Pugh

Kudo ³³

TNM

Child - Pugh

가 gelfoam

가

JIS score 5

JIS score 5 3

JIS

score 5

가

JIS scoring system

0~4

가 , 0~4

가 1

가

가

JIS scoring system

V.

470

gelfoam .

20.8 1 , 2 , 3 , 4 ,

5 66.1%, 45.0%, 34.1%, 28.2%, 22.0% .

JIS score가 ,

, microcatheter , ,

, , , , , ,

, TNM 가 ,

, , , , ,

prothrombin index, , Child - Pugh 가 .

JIS score 가 가

, , , , ,

가 . 5

5 가

microcatheter 15가

. ,

JIS score가 ,

가

1. Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, Nakajima Y, Ohnishi K. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. *Cancer* 1985;56(4):918 - 928.
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Abstract

Analysis of Long Term Survival Rate and Prognostic Factors in Patients with Hepatocellular Carcinoma Treated by Hepatic Arterial Chemoembolization

Seung Hyoung Kim

*Department of Medicine
The Graduate School, Yonsei University*

(Directed by Professor Jong Tae Lee)

Transcatheter arterial chemoembolization (TACE) is the most common treatment method for the patients with hepatocellular carcinoma (HCC), but very diverse survival rates and prognostic factors have been reported. In this study, the long term survival rate and prognostic factors were investigated in patients with HCC treated by TACE with gelfoam embolization, and the role of Japan integrated staging (JIS) score as a prognostic index was also evaluated.

470 HCC patients treated by TACE as the first treatment modality from January 1 1997 to December 31 2001 were enrolled. TACE was accomplished by hepatic arterial infusion of

the mixture of lipiodol and adriamycin, and by gelfoam embolization in all the patients. The survival rates were calculated by the Kaplan-Meier method. Univariate analysis using log-rank test and multivariate analysis using Cox's proportional hazard model were applied to determine which prognostic factors were statistically significant. To reveal the characteristics of the patients survived 5 years or more, the significantly different prognostic factors of them compared with the patients who survived less than 5 years were evaluate by Student t - test, χ^2 - test, and Fisher's exact test.

The median survival period was 20.8 months and annual survival rates were as follows; one - year, 66.1%; two - years 45.0%; three - years, 34.1%, four - years, 28.2% and five - years, 22.0%.

The significant prognostic factors by univariate analysis included JIS scoring system which was very significant, and included the number of treatment, use of microcatheter, collateral artery, tumor necrosis rate(TNR), which were associated with TACE, and included tumor type, number, total size, portal vein thrombosis, extrahepatic metastasis, serum α - fetoprotein, TNM stage, which reflected HCC state, and included serum albumin, serum bilirubin, prothrombin index, ascites, Child - Pugh classification, which reflected liver function. According to multivariate analysis, JIS score, TNR, tumor type, serum α - fetoprotein, the number of treatment were significant in the descending order of odds ratio. The significant prognostic factors

of the patients survived 5years or more were the same as those in univariate analysis except two factors, - fetoprotein and use of microcatheter.

These results suggest that JIS scoring system, reflecting HCC state and liver function simultaneously, will be a good prognostic factor of HCC patient treated by TACE, and that the survival rate is significantly influenced by TNR and the number of TACE.

Key Words : hepatocellular carcinoma; survival rate; prognostic factors; transcatheter arterial chemoembolization