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: Does Meeting Milan's Criteria at the Time of Recurrence Have an Impact on Survival Outcome After Recurrence?

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이 논문을 의학 석사학위신청 논문으로 제출함

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김효신의 석사학위논문을 인준함

위원장 조선대학교 교 수 김 경 종 印

위 원 조선대학교 교 수 김 권 천 印

위 원 조선대학교 부교수 김 성 수 印

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조선대학교 대학원

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초록

간암의 수술적 절제후 재발한 환자에 대한 예후 및 자연경과 분석

: 간암 재발시 밀란기준의 임상적 유용성

김 효 신
지도교수: 김 권 천 교수.
조선대학교 의과대학 외과학 교실

배 경: 간암의 치료에 있어 수술적 접근이 효과가 가장 좋은 것으로 알려져 있다. 간암치료의 수술적 치료중 간이식의 적응증으로 밀란 기준의 유용성은 이미 증명이 되었고 간절제시에도 밀란 기준이 치료 결과를 향상시킨다는 보고가 있다. 그러나 수술적 치료 이후에 간암의 재발이 있는 경우 표준 치료 지침이 없는 상태이다. 이에 수술적 절제 이후 간암 재발시 밀란 기준의 임상적 유용성을 알아보고자 한다.

Methods: 간암으로 인해 수술적 절제를 시행 받은 환자 중에서 재발성 간암이 있는 959명의 환자를 대상으로 간암 재발전후의 상태를 밀란 기준에 따라 4군의 소그룹으로 나누어 분석을 시행하였다.: IN-IN (재발전 수술당시 간암의 형태가 밀란 기준 이내이며 재발시에도 밀란 기준 이내인 그룹) , IN-OUT (재발전 수술당시 간암의 형태가 밀란 기준 이내이며 재발시 밀란 기준을 벗어난 그룹), OUT-IN , OUT-OUT .

Results: 전체 환자군의 1년,3년, 5년간 누적 생존율과 무병생존율은 81%, 55%,45% 과 63%, 46%,42% 로 나타났다. 세부그룹가운데 IN-IN 군에서 다른 그룹에 비해 5년 누적생존율 과 무병생존율이 54% 와 45% 로 높게 나왔다.($P \leq 0.05$), IN-OUT 군과 OUT-IN 군의 5년 누적생존율과 무병생존율은 통계적인 차이를 보이지 않았다. 한편 OUT-OUT 군에서 가장 낮은 누적생존율과 무병생존율을 보였다.(24.8% and 31.9%, P≤ 0.05). 치료방법에 누적 생존율 분석에서 모든 세부그룹에서 Curative intent treatment를 받았던 환자에서 Non-Curative intent treatment 받았던 환자보다 통계적으로 유의한 차이를 보였다.(5-year OS, IN-IN: 63% vs. 45.5, P<0.00; IN-OUT:59% vs.38%, P =0.015; OUT-IN:53.5% vs. 30.7%, P =0.005; OUT-OUT:56.9% vs. 37%, P<0.000).

Conclusion: 밀란 기준은 재발시에도 생존율에 영향을 미치는 인자로 작용하였고 이를 통해 재발시 환자의 예후를 예측하는데 사용할수 있으리라 기대된다. 더불어 재발시에도 가능하면 Curative intent treatment 의 방법으로 치료적 접근을 하는 것이 환자의 생존율을 높이는데 중요하다.

Key words : Milan's criteria, Hepatocellular carcinoma, Curative intent treatment.

Introduction

The detection of early stage hepatocellular carcinoma (HCC) has increased recently due to the implementation of a surveillance program in high-risk populations.[1] As a result, the number of patients targeted for curative treatment for HCC has increased accordingly.

The most effective treatment for HCC is hepatic resection and LT. [2] Even though LT provides a better outcome, it is considerably limited by organ shortage in many cases where HCC is within the Milan criteria. [3] Because of the long wait time for LT, hepatic resection is performed as a bridge treatment to avoid tumor progression prior to salvage LT which affords better survival outcome.[4,5]

Poon et al. reported that up to 79% of patients who received bridge hepatic resection are suitable for salvage LT after recurrence using the same Milan criteria for primary transplantation. [6] Lim et al. also reported that hepatic resection offers good OS for patients with HCC within the Milan criteria and those with good liver function, although recurrence rates remain high. [7] The implication of these findings is that Milan criteria may not be the only useful measure for primary LT.

However, it has not been reported whether the status of HCC at the time of recurrence after primary hepatic resection has an impact on the prognosis. This study focuses on the overall survival(OS) and the re-recurrence free survival (RFS) rates for patients according to the Milan criteria status at the time of recurrence as well as the Milan criteria status at the time the initial hepatic resection.

Method

Patients

Between January 2005 and December 2011, 1,018 patients experienced recurrence after the initial primary hepatic resection for HCC at the Seoul National University Hospital and Samsung Medical Center. Fifty-nine patients were excluded from this analysis for the following reasons: non-primary resection (n=48), extra-hepatic recurrence (n=6), double primary cancer (n=3), and each one of HCC rupture and adjacent organ invasion. Consequently, 959 patients were reviewed.

The study cohort was classified into the following 4 groups according to the status of HCC at the time of the hepatic resection, and at the time of the recurrence after resection: IN-IN MC (inside the MC at the time of the hepatic resection, and inside the MC at the time of the recurrence, n=443), IN-OUT MC (inside the MC at the time of hepatic resection, and outside the MC at the time of recurrence, n=104), OUT-IN MC (outside the MC at the time of hepatic resection, and inside the MC at the time of recurrence, n=287), and OUT-OUT MC (outside the MC at the time ofhepatic resection, and outside the MC at the time of recurrence, n=88) (Figure 1.).

The types and extent of resection were based on the tumor size, location and liver reserve function estimated based on the Child–Pugh score, and the indocyanine green retention rate at 15 min. Curative resection was defined as histologically negative surgical margins and the absence of residual tumor. A major resection was defined as a resection of 3 or more segments and a minor resection was defined as a resection of 2 or fewer segments according to the Couinaud classification.

After hepatic resection, and HCC recurrence, all the patients were regularly followed up every 3-4 months to check for recurrence by monitoring the plasma levels of alpha-fetoprotein (AFP)and proteins induced by vitamin K absence-II (PIVKA-II), and by imaging studies with dynamic computed tomography scans or magnetic resonance imaging. Recurrence was defined as

new lesions observed with at least one imaging method according to EASL and KASL guidelines.[8,9] When recurrence was detected, the patients received further treatment using several modalities, as indicated. Treatment modalities were divided into two groups: curative (hepatic re-resection, radiofrequency ablation therapy, percutaneous ethanol injection, and LT) and non-curative (trans-arterial chemoembolization [TACE], chemotherapy, supportive care, etc.).

Statistical analysis

Statistical analysis was performed using IBM SPSSversion 20 (SPSS Inc., Chicago, IL). Categorical data were compared using Pearson's chi-square test or Fisher's exact test, as appropriate. Continuous data were compared using the Wilcoxon rank-sum test. A *P*-value lower than 0.05 was considered to indicate statistical significance. In the survival analysis, RFS was defined as the interval between the time of the diagnosis of the andre-recurrence, and OS was defined as the interval between the time of recurrence andthe patient's death. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test.

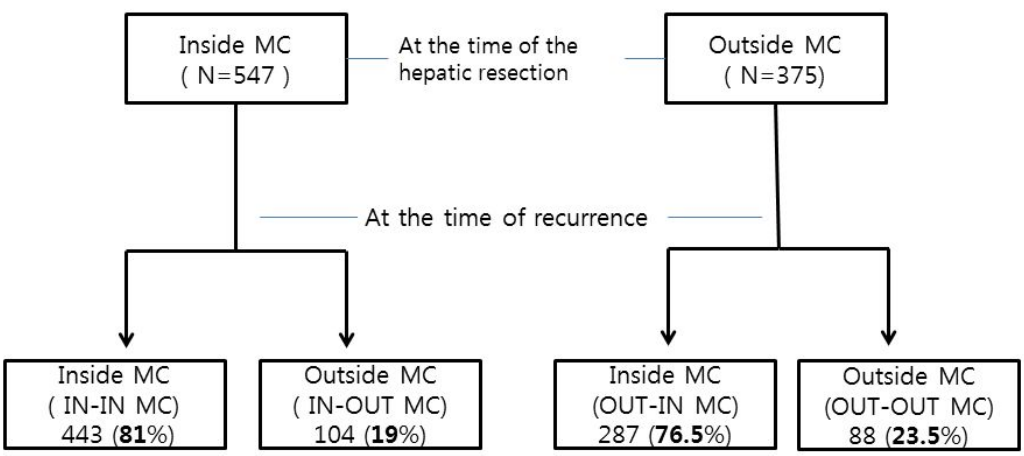


Figure 1. Recurrence status of HCC according to status of HCC at the time of the hepatic resection.

Result

Baseline Characteristics

Table 1 shows the baseline characteristics of the entire cohort. The average age was 54.9± 10.0 years at the time of hepatic resection and 56.0± 10.3 years at the time of recurrence. Eight hundred and two patients (83.6%) were male. Hepatitis B virus infection was the most common etiology (83.0%) for HCC. The proportion of cases within the Child–Pugh A group was over 90% (91.2%) at the 1st occurrence and 84.6% at the time of recurrence.

Mean tumor size at the time of recurrence was1.8± 1.1 cm, which was 4.8 ± 3.4times larger than at the time of hepatic resection. Most of the lesions were solitary (95.1%) at the time of hepatic resection, but the incidence of solitary lesion was 62.6% at the time of recurrence.

Subgroup according to the MC

At the time of the hepatic resection, the proportion of cases within MC was 59.3% and the proportion outside the MC was 40.7%. At the time of recurrence, 80.9% of cases within the MC fell in the IN-IN MC group while 19.1% were in the IN-OUT MC group. The OUT-IN MC group comprised 76.5% of the cases outside the MC at the time of hepatic resection while the OUT-OUT MC group comprised 23.5% (Figure 1.).

1. IN-IN and IN-OUT MC groups

Table 2 shows the baseline characteristics of the IN-IN MC and IN-OUT MC groups. The IN-OUT MC group had larger tumors (> 3cm; 49.0% *vs.* 36.2%) (P = 0.019), and higher serum PIVKA-II levels at the time of hepatic resection (> 40 IU/mL;70.8% *vs.* 48.2%) (P = 0.011). Pathologic results also showed more aggressive tumors in the IN-OUT MC group, specifically,macrovascular invasion (47.6% *vs.* 29.4%, P = 0.002), Edmondson-Steiner grades

III-IV (48.5% *vs.* 33.9%, *P* = 0.006), and positive resection margins (5.9% *vs.* 1.4%, *P* = 0.013).

At the time of recurrence, the IN-OUT MC group had higher serum AFP (> 20 ng/mL; 45.4 % *vs.* 32.9%, *P* = 0.025), and serum PIVKA-II (> 40 IU/mL;36.2% *vs.* 21.0%) levels (*P* = 0.012). However, there was no difference in the rates of application for the curative treatment modality in both groups

2. OUT-IN and OUT-OUT MC groups

The OUT-OUT MC group had multiple tumors on preoperative imaging (> 3; 10.2% *vs.* 2.8%, *P* = 0.007), more vascular invasion on preoperative imaging (21.6% *vs.* 12.2%, *P* = 0.037), and pathologic macrovascular invasion (65.7% *vs.* 37.9%, *P* = 0.000) (Table 2.). At the time of recurrence, the OUT-OUT MC group had larger tumors (> 3cm; 36.8% *vs.* 3.5%, *P* = 0.000), and more tumors (78.4% *vs.* 28.8%, *P* = 0.000) compared to the OUT-IN MC group.

Table 1. Clinical, Operative, and Pathologic Data at Presentation of Primary Tumor

Variable	All Patients (N = 959)	Variable	All Patients (N = 959)
At the time of hepatic resection		**Operative data**	
Age, mean (SD)	54.92(10.0)	Extent of resection	
Male sex, n (%)	802 (83.6)	Minor hepatectomy	475 (49.5)
Underlying liver disease, n (%)		Major hepatectomy	468 (48.8)
HBV	796 (83.0)	Missing, n (%)	16 (1.7)
HCV	38 (4.0)		
Alcohol	13 (1.4)	**Pathologic data**	
Others	111(11.6)	Tumor size, cm	
Missing, n (%)	1 (0.1)	Mean (SD)	4.9 (3.4)
Child-Pugh classification, n (%)		Missing, n (%)	5 (0.5)
A	875 (91.2)	No. tumors	
B	84 (8.8)	Mean (SD)	1.1 (0.5)
BCLC stage at presentation		Multiple tumors, n (%)	83 (8.7)
O	38 (4.0)	Vascular invasion-microscopic	
A	345 (36.0)	Positive, n (%)	486 (50.7)
B	328 (34.2)	Negative, n (%)	473 (49.3)
C	245 (25.5)	Histologic grade, ES –Worst grade *	
Missing, n (%)	3 (0.3)	I,II	574 (59.9)
Milan criteria		III,IV	383 (39.9)
Within, n (%)	580 (60.5)	Missing, n (%)	2 (0.2)
Beyond, n (%)	379 (39.5)	Margin	
Missing, n (%)	.	Positive, n (%)	28 (2.9)
Tumor size on imaging, cm			
Mean (SD)	4.8 (3.4)	**At the time of Recurrence**	
Missing, n (%)	6 (0.6)	Age, mean (SD)	56.02(10.3)
Tumor size on imaging, cm		Child-Pugh classification, n (%)	
≤ 3	377 (39.3)	A	84.6
> 3	576 (60.1)	B	5.5
Tumor size on imaging, cm		Missing, n (%)	9.9
≤ 5	653 (68.1)	AFP, ng/mL	
> 5	300 (31.3)	Mean (SD)	3192.6 (22901.2)
No. tumors imaging		>20 , n (%)	339 (35.3)
Mean (SD)	1.2 (0.8)	Missing, n (%)	63 (6.6)
Single	912 (95.1)	PIVKA,, ng/mL	
Multiple	47 (4.9)	Mean (SD)	479.0 (3779.1)
No. tumors imaging		>40 , n (%)	176 (18.7)

≤ 3	942 (98.2)	Missing, n (%)	313 (32.6)
> 3	17 (1.8)	Tumor size on imaging, cm	
Vascular invasion on imaging, n(%)		Mean (SD)	1.8 (1.184)
Positive	54 (5.6)	Missing, n (%)	34 (3.5)
Negative	905 (94.4)	Tumor size on imaging, cm	
AFP, ng/mL		≤ 3	812 (84.7)
Mean (SD)	5428.4 (33905.0)	> 3	113 (11.8)
>20 , n (%)	524 (54.6)	Tumor size on imaging, cm	
>200 , n (%)	288 (30.0)	≤ 5	872 (90.9)
Missing, n (%)	57 (5.9)	> 5	53 (5.5)
PIVKA,, ng/mL		No. tumors imaging	
Mean (SD)	1751.1 (7781.7)	Mean (SD)	2.21 (2.390)
>40 , n (%)	449 (46.8)	Multiple tumors, n (%)	359 (37.4)
Missing, n (%)	276 (28.8)	Missing, n (%)	27 (2.8)
Total bilirubin, mg/dL		Site of recurrence	
> 1.2	164 (17.1)	Intrahepatic	953 (99.4)
INR		Intra- and Extrahepatic	6 (0.6)
> 1.0	672 (70.1)	Treatment modality	
Missing, n (%)	9 (0.9)	Embolization	549 (57.2)
Creatinine, mg/dL		Repated Resection	66 (6.9)
> 1.4	30 (3.1)	Ablation	256 (26.7)
Missing, n (%)	2 (0.2)	PEI	40 (4.2)
Albumin, g/dL		Transplantation	25 (2.6)
≤ 3.5	114 (11.9)	Missing, n (%)	23 (2.4)
Platelet count, x 103/ μL		Milan criteria	
≤ 100	164 (17.1)	Within, n (%)	752 (78.4)
ICG R15		Beyond, n (%)	169 (17.6)
Mean (SD)	12.9 (9.3)	Missing, n (%)	38 (4.0)
> 10	506 (58.6)		
> 20	106 (12.1)		
Missing, n (%)	95 (9.9)		

*Edmonson-steiner Worst grade

Table 2. Characteristics and Clinical data between IN-OUT MC and IN-IN MC group.

Variable	IN-Out Milan	IN-IN Milan	P	OUT-OUT Milan	OUT-IN Milan	P
At the time of hepatic resection						
Age, mean (SD)	75 (72.1)	330 (74.5)	0.621	55 (62.5)	203 (70.7)	0.150
Male sex, n (%)	85 (81.7)	374 (84.4)	0.553	71 (80.7)	242 (84.3)	0.416
Underlying liver disease, n (%)						
HBV	74 (80.4)	334 (82.9)	0.548	64 (86.5)	192 (78.7)	0.180
HCV	10 (10.1)	42 (9.8)	1.000	3 (3.6)	22 (7.9)	0.222
Child-Pugh classification, n (%)						
B	10 (9.6)	26 (5.9)	1.860	9 (10.2)	38 (13.2)	0.581
BCLC stage OA vs BCD						
BCD	47 (45.2)	157 (35.4)	0.072	82 (93.2)	272 (95.8)	0.392
Tumor size on imaging, cm						
> 3	51 (49.0)	159 (36.2)	0.019	80 (90.9)	266 (93.3)	0.481
Tumor size on imaging, cm						
> 5				63 (71.6)	226 (79.3)	0.145
No. tumors imaging						
Multiple	0 (0.0)	12 (2.7)	0.135	13 (14.8)	21 (7.3)	0.053
No. tumors imaging						
> 3				9 (10.2)	8 (2.8)	0.007
Vascular invasion imaging, n (%)						
Positive				19 (21.6)	35 (12.2)	0.037
AFP, ng/mL						
>20 , n (%)	62 (60.2)	224 (54.8)	0.375	52 (59.8)	171 (62.9)	0.614
>200 , n (%)	36 (35.0)	107 (26.2)	0.086	32 (36.8)	105 (38.6)	0.801
PIVKA,, ng/mL						
>40 , n (%)	51 (70.8)	147 (48.2)	0.001	57 (82.6)	176 (85.0)	0.702
>200 , n (%)	21 (29.2)	66 (21.6)	0.213	45 (65.2)	137 (66.2)	0.884
Total bilirubin, mg/dL						
> 1.2	13 (12.5)	81 (18.3)	0.194	13 (14.8)	53 (18.5)	0.523
INR						
> 1.0	72 (69.2)	338 (76.6)	0.130	61 (70.9)	178 (63.1)	0.199
Creatinine, mg/dL						
> 1.4	0 (0)	16 (3.6)	0.051	1 (1.1)	13 (4.5)	0.203
Albumin, g/dL						
≤ 3.5	9 (8.7)	55 (12.4)	0.315	9 (10.2)	39 (13.6)	0.470
Platelet count, x 103/ μL						
≤ 100	17 (16.3)	87 (19.6)	0.490	15 (17.0)	41 (14.3)	0.500
ICG R15						
> 10	58 (64.4)	242 (59.9)	0.475	37 (46.8)	148 (58.3)	0.090
> 20	17 (18.1)	51 (12.6)	0.182	13 (16.2)	24 (9.3)	0.100
Postoperative data						
AFP, ng/mL						
>20 , n (%)	37 (38.1)	103 (24.6)	0.011	38 (46.9)	104 (38.8)	0.190
PIVKA,, ng/mL						
> 40, n (%)	8 (16.0)	29 (11.3)	0.347	12 (27.9)	47 (30.1)	0.850
Pathologic data						
Vascular invasion-microscopic						
Positive, n (%)	59 (56.7)	209 (47.2)	0.082	49 (55.7)	141 (49.1)	0.330

Vascular invasion-Macroscopic						
Positive, n (%)	40 (47.6)	111 (29.4)	0.002	46 (65.7)	81 (37.9)	0.000
Edmonson-steiner Worst grade						
III,IV	50 (48.5)	150 (33.9)	0.006	38 (43.2)	157 (54.9)	0.060
Margin						
Positive, n (%)	6 (5.9)	6 (1.4)	0.013	3 (3.4)	13 (4.6)	1.000
At Time of Recurrence						
AFP, ng/mL						
>20 , n (%)	44 (45.4)	138 (32.9)	0.025	40 (50.6)	107 (40.0)	0.120
PIVKA,, ng/mL						
>40 , n (%)	25 (36.2)	63 (21.0)	0.012	24 (42.9)	64 (33.3)	0.210
Tumor size on imaging, cm						
> 3	46 (44.2)	25 (5.6)	0.000	32 (36.8)	10 (3.5)	0.000
Tumor size on imaging, cm						
No. tumors imaging						
Multiple tumors, n (%)	83 (80.6)	118 (26.8)	0.000	69 (78.4)	82 (28.8)	0.000
Treatment modality						
Non-Curative intent	61 (59.2)	217 (49.9)	0.100	57 (65.5)	193 (68.2)	0.690
Curative intent	42 (40.8)	218 (50.1)		30 (34.5)	90 (31.8)	

OS and RFS rates

1. Entire cohort

The entire cohort of 959 patients who had recurrent HCC after the hepatic resection had respective 1-, 3-, and 5-year OS of 81.0%,55.7%, and 45.8%, and 1-, 3-, and 5-year RFS of 63.7%, 46.1%, and 42.0%after the recurrence (Figure 2.).

2. Subgroup

The IN-IN MC group had the best outcome among the subgroups with respect to the 5-year OS and RFS (54.5% and 45.7%, $P \leq 0.05$). There was no statistical difference between the IN-OUT and OUT-IN MC groups with respect to the 5-year OS (46.1% and38.6%) and RFS (37.5% and 36.6%). The OUT-OUT MC group had worse outcomesfor the 5-year OS and RFS (24.8% and 31.9%, $P \leq 0.05$) (Figure 3.).

3. According to treatment modality

All subgroups showed better OS outcomes with the curative treatment after the recurrence (Figure4.). Only the OUT-IN MC group showed a better outcome for the 5-year RFS (40.2% *vs.* 34.2%, $P = 0.007$).

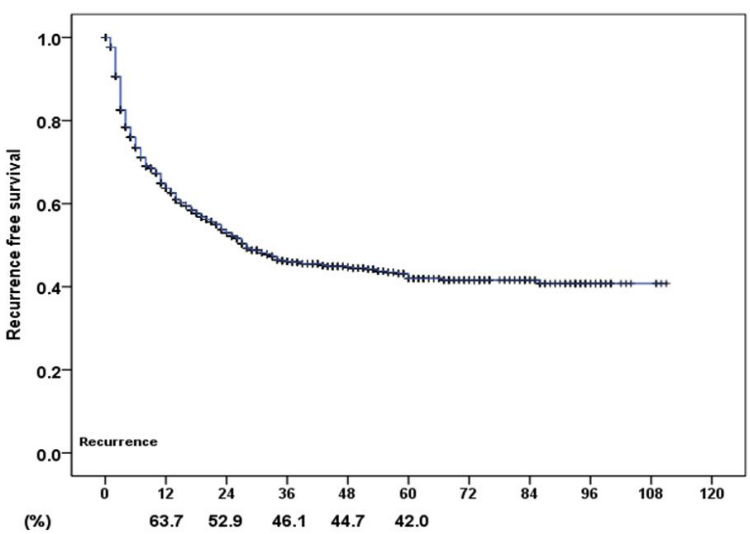


Figure 2. Survival and the re-recurrence free survival rates after the recurrence of entire cohort.

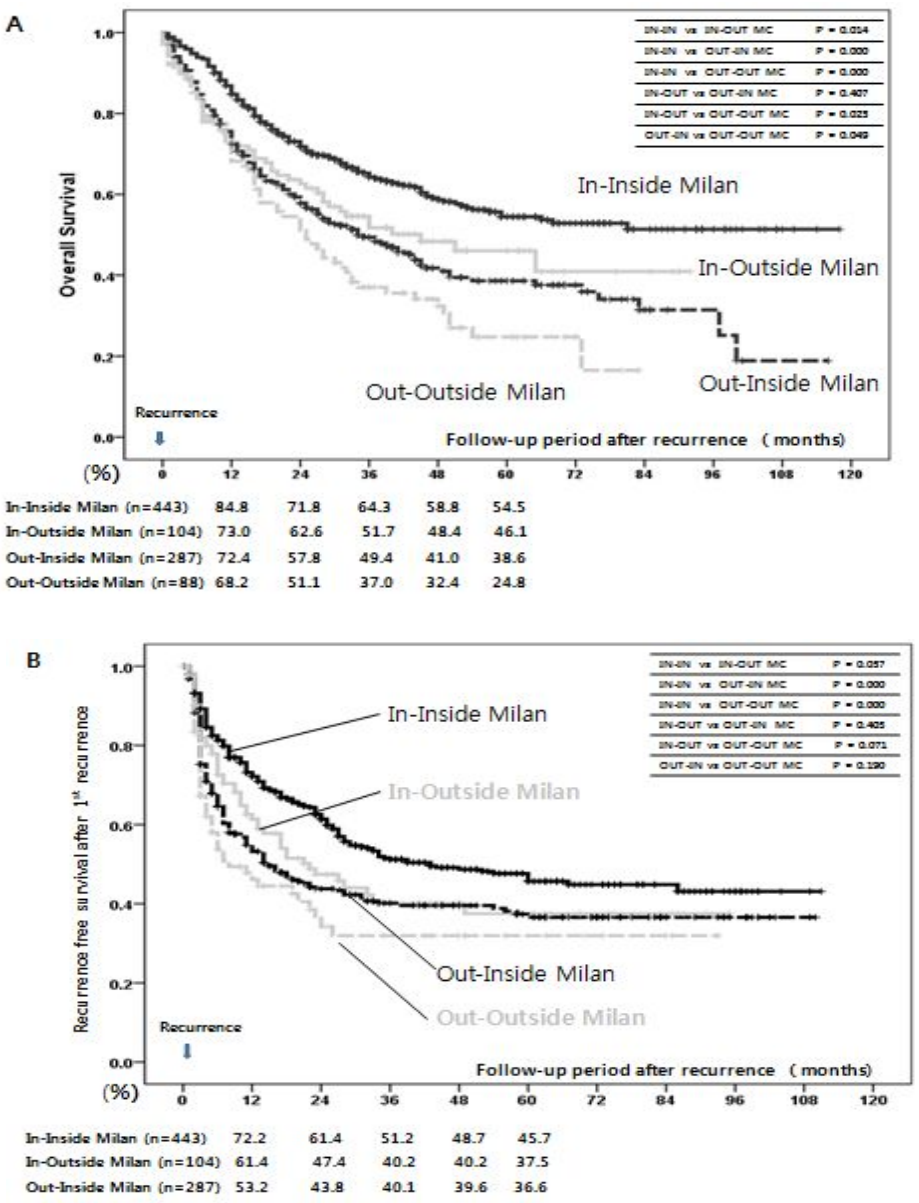


Figure 3. Survival and the re-recurrence free survival rates after the recurrence of subgroups. A, Overall survival B, re-recurrence free survival

Discussion

In order to evaluate whether the status of HCC at the time of recurrence after primary hepatic resection has an impact on the prognosis, we divided our entire cohort into four subgroups classified according to the status of recurrence in two situations, i.e., at the time of hepatic resection and at the time of the recurrence and analyzed the outcomes for these subgroups.

One interesting result wasthat the rate of recurrence within the MC was high, regardless of the MC status of the primary tumor. In this study, 81% of patients whose primary HCC was within the MC developed recurrence within the MC, while 77% of patients with primary HCC beyond the MC developed recurrence within the MC (Figure 1.). Kamiyama et al. reported different results, with IN-IN MC recurrence of 74% and OUT-IN MC recurrence of 50%.[10] This result was mainly caused by the differences in patient characteristics. In our cohort, the initial treatment was hepatic resection rather than preoperative TACE, which was used for approximately 34% of patients in the other study. In addition, the underlying disease was hepatitis B viral infection for 83% of our patients rather than 38% in the previous study.

Even after recurrence (as in the study cohort),the 5-year OS for patients with IN-IN MC recurrence (45.7%) was similar to that in the previous report, in which the 5-year OS was 52% after hepatic resection in patients with early HCC without recurrence. [11,12] Furthermore, the survival outcomes for the OUT-IN MC group were not different from those of the IN-OUT MC group, which also had favorable outcomes (the 5-year OS was 38.6%*vs*.46.1%). These findings suggest that even patients whose primary HCC was beyond the MC can have favorable outcomes in the patients whose recurrence is within the MC.

Even though various therapeutic modalities have been used to treat recurrent HCC. There is no standard strategy for choosing between different modalities. Thomas et al. reported the outcome s of treatment modalities for recurrent HCC which was categorized based on morphology and Del Gaudio et al. timing of recurrence.[13][14] However, the outcome of type of MC is unknown.

Therefore, we investigated the outcomes of treatment modality in our four subgroups. Curative intent treatment showed better OS in all subgroups. However, the only OUT-IN showed satisfactory response to the curative treatment in re-RFS (Figure 5.). To the best of our knowledge, this is the first study to evaluate the outcomes for the OUT-IN group. According to our results, if tumor recurrence is within MC in the patient whose previous tumor status was beyond the MC, curative treatment can improve the patient's prognosis for both OS and re-RFS.

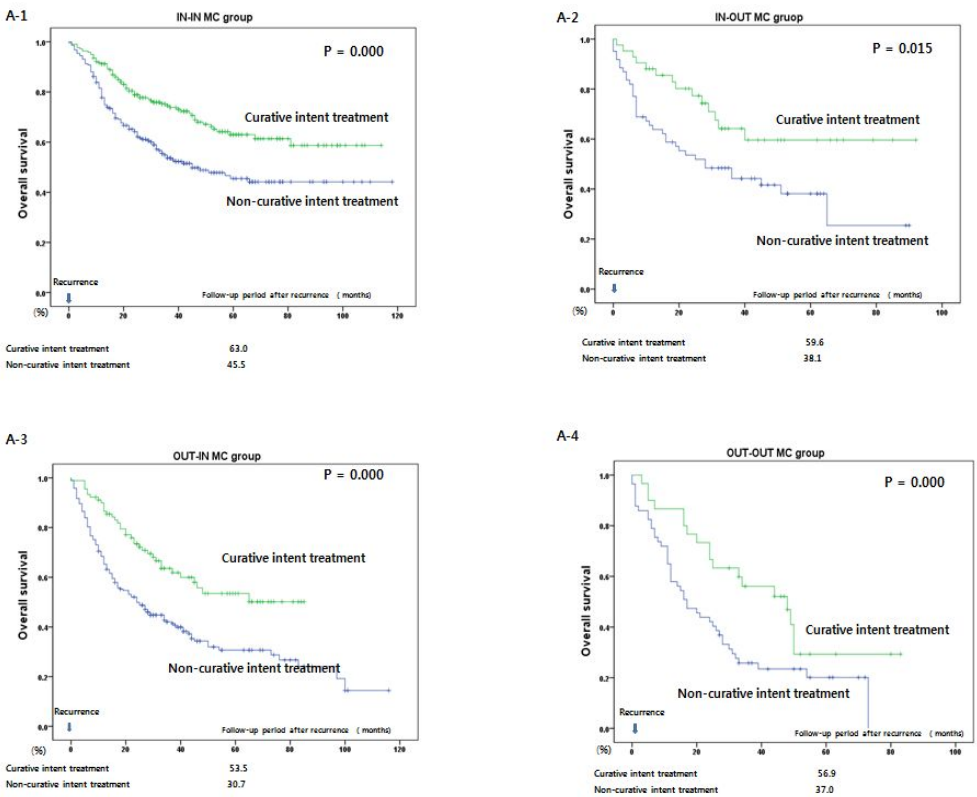


Figure 4. Survival rates of subgroups according to treatment modalities after the recurrence

A-1. OS of IN-IN MC; A-2, OS of IN-OUT MC; A-3, OS of OUT-INT MC; A-4, OS of OUT-OUT MC

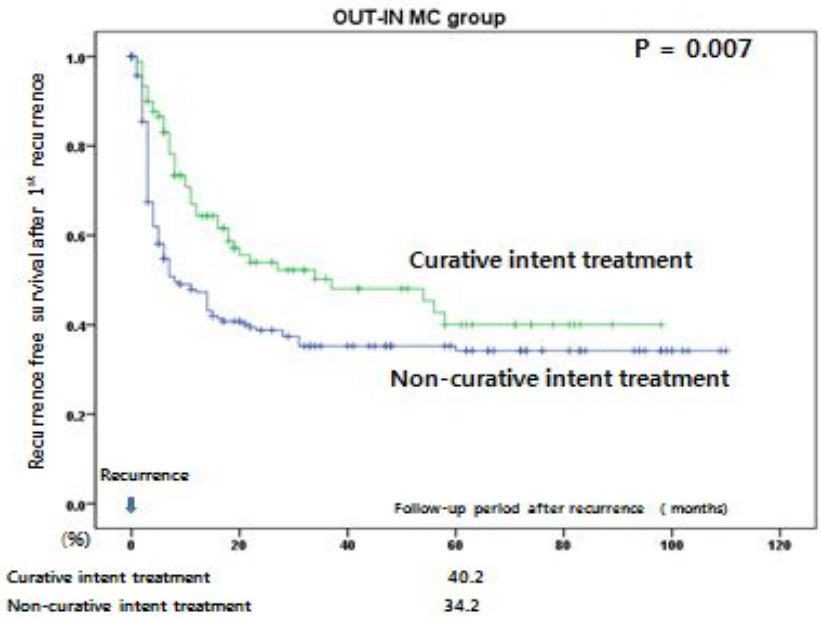


Figure 5. the re-recurrence free survival rates of OUT-IN MC group according to treatment modalities after the recurrence.

Based on these results, we hypothesized that identifying the predictive factors for OUT-OUT MC recurrence would be invaluable for developing a treatment plan and understanding future prognosis. The results of the analysis showed that the predictive risk factors for OUT-OUT MC were ICG R15 > 20% and tumors>3 (Table3.).Therefore, preemptive LT should be considered in the clinical setting for patients without the above risk factors and with HCC beyond the MC.

After the recurrence, 50.3 %of entire cohort experienced re-recurrence during follow up period. When patients with re-recurrence were divided by the Milan criteria again, the rate of IN MC re-recurrence is still high (Figure.6). And also IN MC showed better survival than OUT MC at the re-recurrence which is similar to our previous subgroup results (Figure.7). It should be noted that the IN MC group includes OUT-OUT, OUT-IN and IN-OUT MC in addition to IN-IN MC subgroup. This means that if the patient showed IN MC re-recurrence, even though

previous status MC was outside(OUT-OUT, OUT-IN and IN-OUT), OS is as good as IN-IN MC group.

Based on this result, we analyze survival outcome again with the number of IN-MC in order to know whether the number of IN-MC has impact on survival outcome. Total number of IN-MC is two and above showed significant better survival outcome than zero and one IN-MC in number (Figure.8)

Table 3. Multivariate analysis of the predictive factor for the recurrence of OUT-OUT MC among the Outside MC group at the time of hepatic resection by logistic regression model.

Variable at Presentation	OR	95% CI	P
Age >60 years	1.117	0.578-2.158	0.742
Male Sex	0.882	0.39-1.997	0.764
HBV	0.812	0.316-2.081	0.664
HCV	1.222	0.3-4.978	0.78
BCLC_BCD	1.302	0.305-5.548	0.722
CTP B	1.783	0.53-5.998	0.35
TB >1.2	1.487	0.585-3.778	0.404
INR >1.0	0.654	0.333-1.286	0.218
Size > 5cm	1.222	0.409-3.657	0.72
Size > 6cm	0.911	0.372-2.231	0.838
Number > 3	0.172	0.043-0.688	0.013
Major VI(+)	0.681	0.269-1.722	0.417
ICG R-15 >20	0.383	0.157-0.932	0.034

Note: variable was included if P value is below 0.5 in univariate analysis; OR, odds ration

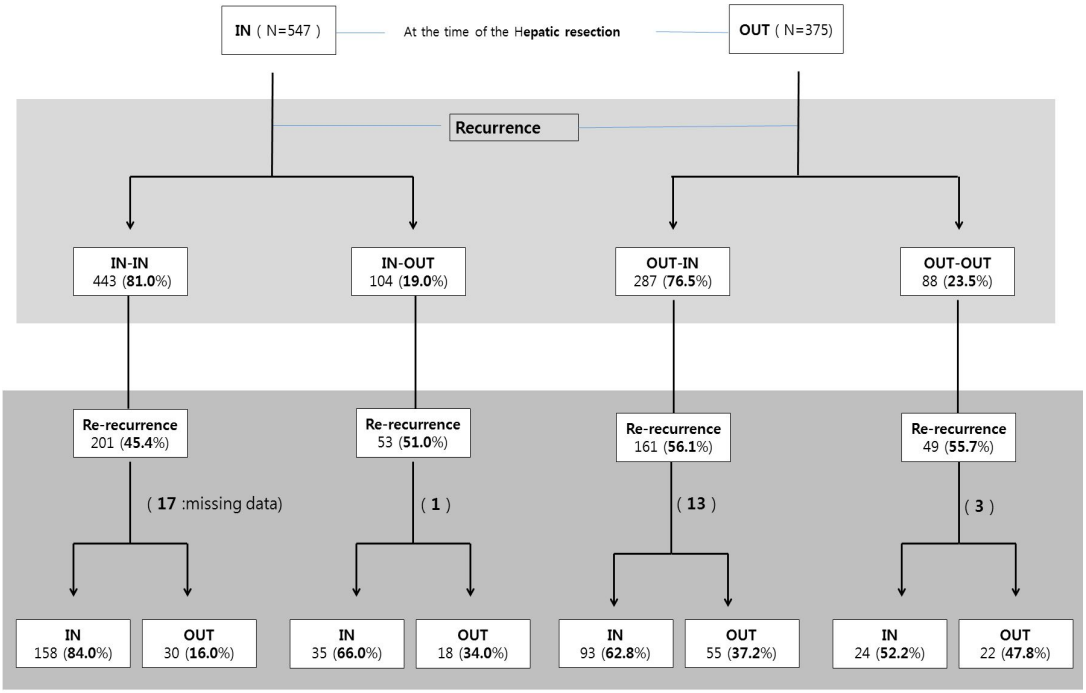


Figure 6. HCC status according to Milan's criteria from recurrence to re-recurrence

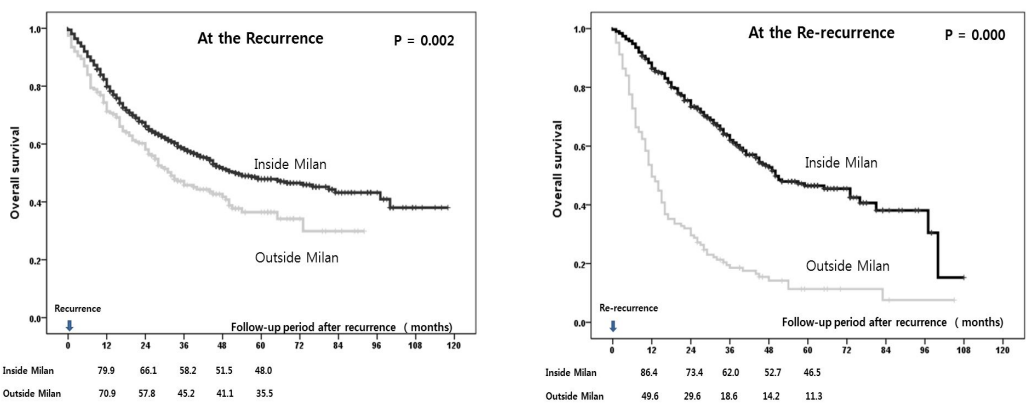
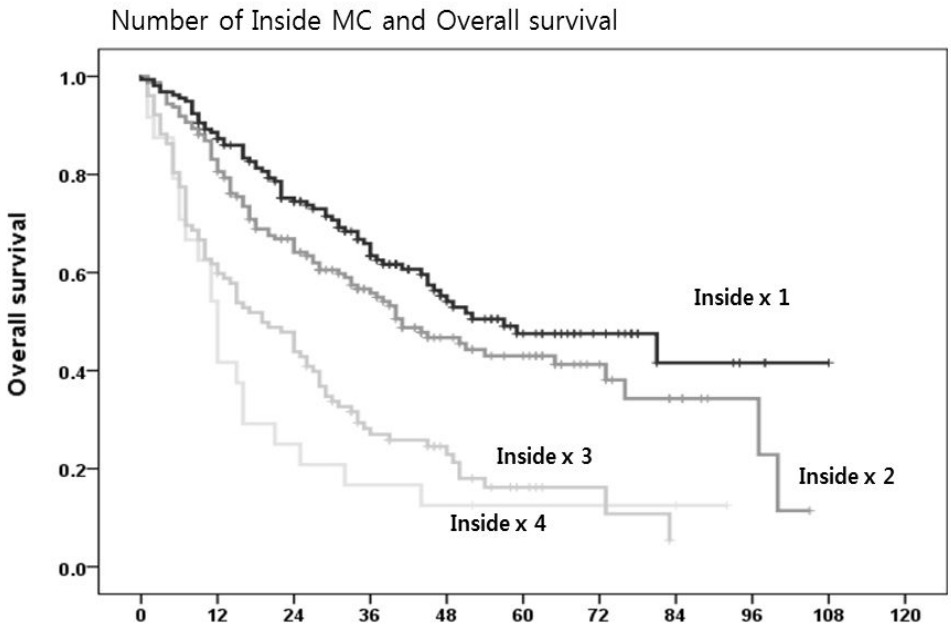


Figure 7. Overall survival rate according to Milan's criteria in Each time.

A, At the time of recurrence ; B, At the time of re-recurrence



IN x0	54.2	25.0	16.7	12.5	12.5	
IN x1	59.8	43.9	27.0	22.9	16.2	P = 0.297
IN x2	80.6	64.1	55.8	46.7	43.0	P = 0.000
IN x3	87.3	74.5	63.4	54.1	47.5	P = 0.000

Figure 8. Overall survival according to number of Inside Milan's criteria from At the time of surgery , recurrence to re-recurrence.

Conclusion

To summarize our study, first, the prognosis for recurrent HCC in patients who had undergone an initial hepatic resection was not poor; the 5-year OS and the re-RFS were 45.8% and 42.0%, respectively. Second, over 75% of recurrent HCC cases were within the MC regardless of the previous MC status at the time of the hepatic resection. Third, the survival outcome was affected by the MC at the time of both the resection and the re-recurrence after curative resection. Fourth, curative treatment improved the OS even after HCC recurrence, regardless of the type of recurrence. Furthermore, only the OUT-IN MC group benefitted from curative treatment in terms of both OS and re-RFS.

Reference

[1] Kiyosawa K, Umemura T, Ichijo T, Matsumoto A, Yoshizawa K, Gad A, et al. Hepatocellular carcinoma: Recent trends in Japan. Gastroenterology 2004;127:S17–S26. doi:10.1053/j.gastro.2004.09.012.

[2] Portolani N, Coniglio A, Ghidoni S, Giovanelli M, Benetti A, Tiberio GAM, et al. Early and Late Recurrence After Liver Resection for Hepatocellular Carcinoma: Prognostic and Therapeutic Implications. Annals of Surgery 2006;243:229.

[3] Bhangui P, Allard MA, Vibert E, Cherqui D, Pelletier G, Cunha AS, et al. Salvage Versus Primary Liver Transplantation for Early Hepatocellular Carcinoma: Do Both Strategies Yield Similar Outcomes. Ann Surg 2016;264:155–63. doi:10.1097/SLA.0000000000001442.

[4] Adam R, Azoulay D, Castaing D, Eshkenazy R, Pascal G, Hashizume K, et al. Liver Resection as a Bridge to Transplantation for Hepatocellular Carcinoma on Cirrhosis: A Reasonable Strategy? Annals of Surgery 2003;238:508.

[5] Belghiti J, Cortes A, Abdalla EK, Régimbeau J-M, Prakash K, Durand F, et al. Resection Prior to Liver Transplantation for Hepatocellular Carcinoma. Annals of Surgery 2003;238:885.

[6] Poon RT-P, Fan ST, Lo CM, Liu C-L, Wong J. Long-Term Survival and Pattern of Recurrence After Resection of Small Hepatocellular Carcinoma in Patients With Preserved Liver Function: Implications for a Strategy of Salvage Transplantation. Annals of Surgery 2002;235:373.

[7] Lim KC, Chow PKH, Allen JC, Siddiqui FJ, Chan ESY, Tan SB. Systematic review of outcomes of liver resection for early hepatocellular carcinoma within the Milan criteria. British Journal of Surgery 2012;99:1622–9. doi:10.1002/bjs.8915.

[8] Korean Association for the Study of the Liver. KASL Clinical Practice Guidelines: Management of chronic hepatitis B. Clin Mol Hepatol 2012;18:109–62. doi:10.3350/cmh.2012.18.2.109.

[9] European Association For The Study Of The Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012;57:167–85. doi:10.1016/j.jhep.2012.02.010.

[10] Kamiyama T, Nakanishi K, Yokoo H, Kamachi H, Tahara M, Suzuki T, et al. Recurrence patterns after hepatectomy of hepatocellular carcinoma: implication of Milan criteria utilization. Ann Surg Oncol 2009;16:1560–71. doi:10.1245/s10434-009-0407-7.

[11] Zhu Q, Yuan B, Qiao G-L, Yan J-J, Li Y, Duan R, et al. Prognostic factors for survival after hepatic resection of early hepatocellular carcinoma in HBV-related cirrhotic patients. Clin Res Hepatol Gastroenterol 2016;40:418–27. doi:10.1016/j.clinre.2015.12.007.

[12] Poon RT-P, Fan ST, Lo CM, Liu C-L, Ng IO-L, Wong J. Long-Term Prognosis After Resection of Hepatocellular Carcinoma Associated With Hepatitis B–Related Cirrhosis. Journal of Clinical Oncology 2016. doi:10.1200/jco.2000.18.5.18.issue-5;page:string:Article/Chapter.

[13] Saraswat VA, Pandey G, Shetty S. Treatment Algorithms for Managing Hepatocellular Carcinoma. J Clin Exp Hepatol 2014;4:S80–9. doi:10.1016/j.jceh.2014.05.004.

[14] Del Gaudio M, Ercolani G, Ravaioli M, Cescon M, Lauro A, Vivarelli M, et al. Liver Transplantation for Recurrent Hepatocellular Carcinoma on Cirrhosis After Liver Resection: University of Bologna Experience. American Journal of Transplantation 2008;8:1177–85. doi:10.1111/j.1600-6143.2008.02229.x.