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RAPID COMMUNICATION

Selection of treatment modality for hepatocellular carcinoma according to the modified Japan Integrated Staging score

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Abstract

AIM: To compare the prognosis of patients who underwent hepatectomy and ablation using the modified Japan Integrated Staging score (mJIS).

METHODS: We examined the clinicopathologic records and patient outcomes in 278 HCC patients including 226 undergoing hepatectomy and 52 undergoing ablation therapy.

RESULTS: Cirrhosis was more frequent in the ablation group. Tumor size, number and presence of vascular invasion were significantly higher in the operation group compared to the ablation group. The local recurrence rate adjacent to treated lesions was significantly higher in the ablation group compared to the operation group ($P < 0.05$). The 3- and 5-year survival rates in the ablation and the operation group were 66% and 78%, and 50% and 63%, respectively, but not significantly different. Over 50% survival rates were observed in patients with a mJIS score of 0-2 in both groups. However, survival rates with a score of 3-5 in both groups were significantly lower.

CONCLUSION: According to the mJIS system, both local treatments could be selected for patients with a score of 0-2. However, for patients with a score more than 3, liver transplantation might be a better option in patients with HCC.

Key words: Hepatocellular carcinoma; Hepatectomy, Ablation; Modified Japan integrated staging score; Liver transplantation

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INTRODUCTION

Although hepatic resection is supposed to be the best curative local treatment for hepatocellular carcinoma (HCC)[1-3], sufficient hepatic functional reserve is necessary. In recent years, various treatment modalities have become available for HCC patients and the appropriate treatment should be selected according to tumor staging and liver function[4]. In the past decade, combined staging systems with tumor factors and liver function in HCC patients have been proposed worldwide[4-7]. We also proposed the modified cancer of the liver Italian program (mCLIP) score and the modified Japan Integrated Staging score (mJIS)[8,9]. Comparing the various staging systems using multivariate survival analysis, mJIS is the best available system to predict survival in HCC patients after hepatectomy[10]. The Liver Cancer Study Group of Japan subsequently showed that the mJIS system had good predictive accuracy for survival of Japanese patients with HCC by the records of 42269 patients diagnosed with HCC registered between 1992 and 1999 in a nationwide Japanese database[11].

Liver transplantation (LT) has recently been considered a good option to cure some HCC patients with poor hepatic function, such as Child-Pugh C cirrhosis[12]. The usefulness of cadavaric liver transplantation (LT) for HCC treatment has been clarified in Western countries[13] and, furthermore,

Todo *et al* reported good results in HCC treatment with the living related LT in Japan[14]. Therefore, LT seems to be a better treatment option in some patients who undergo local treatments in Japan. At this stage, Milan or University of California, San Francisco (UCSF) criteria using tumor factors and the Barcelona Clinic Liver Cancer (BCLC) system using tumor, liver function and performance status, have been used to decide the indication of LT[4,15,16]. It has not yet been clarified whether the mJIS system could be useful in the selection of LT in HCC patients.

In this study, we compare patient demographics, preoperative liver function, tumor parameters and long-term patient survival prognosis of 278 HCC patients who underwent hepatectomy and ablation using mJIS at several cancer institutions in Nagasaki prefecture, Japan. We then discuss the selection of treatment by comparing results by LT. Our aim is to clarify the treatment selection criteria for HCC patients using mJIS.

Table 1A Definition and criteria of the TNM stage for HCC according to the Liver Cancer Study Group of Japan[17]

Factor of T category	
1 Number of tumors: 1	
2 Tumor size: no more than 2 cm	
3 No vascular or bile duct invasion	
T category	T1: Fulfilling all three factors
	T2: Fulfilling two factors
	T3: Fulfilling one factor
	T4: Fulfilling none of the factors
N category	N0: Absence of lymph node metastasis
	N1: Presence of lymph node metastasis
M category	M0: Absence of distant metastasis
	M1: Presence of distant metastasis
Stage Ⅰ	T1 N0 M0
Stage Ⅱ	T2 N0 M0
Stage Ⅲ	T3 N0 M0
Stage Ⅳ-A	T4 N0 M0 or T1-T4, N1M0
Stage Ⅳ-B	T1-4, N0 or 1, M1

MATERIALS AND METHODS

Patients

We analyzed 278 patients with HCC who underwent surgical resection or ablation treatments in the Division of Surgical Oncology and the First and Second Department of Internal Medicine, Nagasaki University Graduate School of Biomedical Sciences (NUGSBS), and its related hospitals between 1994 and 2005. The study design was approved by the Human Ethics Review Board of our institution. Informed consent for data collection was obtained from each patient during this period. Anesthetic and patient data were retrieved from the NUGSBS database. Tumor stage and curability were determined according to the *Classification of Primary Liver Cancer*[17]. Subjects were divided into two groups: (1) Operation group with 226 patients. Preoperative treatment was performed in 78 patients including chemoembolization in 69 and thermal ablation in nine. Operative procedures included hemihepatectomy in 56 patients, anatomical sectriectomy in 74 and partial resection in 96. (2) Ablation group with 52 patients, including alcohol injection in 15 patients, radio-frequency ablation (RFA) in 32, and microwave coagulation therapy (MCT) in five patients.

Treatment indications, procedures and follow-up

The volume of liver to be resected was estimated according to results of the indocyanine green retention rate at 15 min (ICG R15) using Takasaki's formula[18]. Furthermore, hepatic function for hepatectomy was limited as ICGR15 < 40%, Child-Pugh classification A or B, and total bilirubin level < 2 mg/dL according to Miyagawa's criteria[19]. The expected liver volume for resection, excluding the tumor (cm^3), was measured by computed tomography (CT) volumetry[20]. Radical hepatectomy was performed to remove the hepatic tumor without leaving any residual tumor. The indications for hepatic resection of the size and the number of HCC were more than 2 cm, and less than or equal to three lesions, respectively. Distant metastasis was an extra-indication for hepatectomy. The assessment of tumor factors in the operation group was confirmed by histopathological examination of the resected specimen. We used the histopathological factors and curability by hepatectomy of the *Liver Cancer Study Group of Japan* by the *Classification of Primary Liver Cancer*[17].

For RFA or MCT, the indication for hepatic resection of the size and the number of HCC were less than 3 cm, and less than or equal to three lesions, respectively[21]. Hepatic function for ablations is limited as Child-Pugh classification A or B, platelet counts more than 50 000/mm^3, prothrombin activity more than 50% and total bilirubin level less than 3 mg/dL. When the appropriate coagulation was estimated to be incomplete by percutaneous puncture, ablations under laparoscopy, thoracoscopy or laparotomy were selected[22,23]. Evaluation of vascular involvement was performed by image analysis, such as enhanced computed tomography or magnetic resonance imaging.

After discharge from hospital, the patient status, laboratory data, and disease recurrence were checked every two to three months.

Staging criteria of the modified Japan Integrated Staging score (mJIS)

The assessment of each factor was confirmed by histopathological examination of the resected specimen, or by computed tomography scan, ultrasonography, magnetic resonance image or angiography. We used the pathological tumor-node-metastasis (pTNM) classification system of the Liver Cancer Study Group (LCSG) of Japan in 2000[17]. T category is determined by three factors of number, size and vascular or bile duct invasion. N category is the presence of lymph node metastasis and M category is the presence of distant metastasis. TNM staging has four stages according to T, N and M categories (Table 1A). Classification of Child-Pugh[24] and liver damage grade by LCSG[17] are shown in Table 1B. The original JIS score proposed by Kudo *et al* comprised the sum of points for two variables of the Japanese TNM classification and Child-Pugh classification[6]. In the modified JIS score proposed by our institute[9,10], the Child-Pugh classification score was replaced by that of liver damage grade by the LCSG of Japan (Table 1C).

Table 1B Definition and criteria of Child-Pugh classification and liver damage grade

Child-Pugh classification[24]	A	B	C
Encephalopathy	none	mild	coma
Ascites	none	responsive	unresponsive
Serum bilirubin (mg/dL)	< 2.0	2.0-3.0	> 3.0
Serum albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
Prothrombin activity (%)	> 70	40-70	< 40
Liver damage grade[17]	A	B	C
Ascites	none	responsive	unresponsive
Serum bilirubin (mg/dL)	< 2.0	2.0-3.0	> 3.0
Serum albumin (g/dL)	> 3.5	3.0-3.5	< 3.0
ICG R15 (%)	< 15	15-40	> 40
Prothrombin activity (%)	> 80	50-80	< 50

Table 1C Definition and criteria of the JIS and the mJIS

	Score			
	0	1	2	3
Original JIS score[6]				
Japanese TNM stage	I	II	III	IV
Child-Pugh Classification	A	B	C	
Modified JIS score[9]				
Japanese TNM stage	I	II	III	IV
Liver damage grade	A	B	C	

TNM: Tumor-node metastasis.

Statistical analysis

Continuous data were expressed as the mean ± SD. Data from different groups were compared using one-way analysis of variance (ANOVA) and examined by student's *t*-test or Dunnet's multiple comparison test. For univariate analysis, categorical data were analyzed by the Fisher's exact test. Disease-free and overall survival rates were calculated according to the Kaplan-Meier method, and differences between groups were tested for significance using the log-rank test. Multivariate analysis was performed using the proportional hazards regression model. A two-tailed *P* value of < 0.05 was considered significant. Statistical analyses were performed using SAS software (Statistical Analysis System Inc., Cary, NC).

RESULTS

Patient age, gender and period of treatment were not significantly different between groups (Table 2). Rates of cirrhosis and Child-Pugh B were significantly higher in the ablation group. Thirty-five percent of patients underwent pretreatment in the operation group; however, no patients underwent other treatments in the ablation group. Tumor size in the operation group was significantly larger than that in the ablation group. The number of tumors and rate of vascular involvement were significantly higher in the operation group compared to the ablation group. Posttreatment adjuvant treatments were similarly performed in both groups.

In the ablation group, tumor relapse was observed in 22 patients (42%) including 10 with intrahepatic metastasis and 12 with local recurrence adjacent to the ablated site (Figure 1). On the other hand, in the operation group, tumor relapse was observed in 122 patients (62%), which included 117 with intrahepatic metastasis and five with local recurrence adjacent to the resected margin. The local recurrence rate adjacent to the treated lesion was significantly higher in the ablation group compared to the operation group ($P < 0.05$).

By applying mJIS, discrimination of survival in each score was remarkable (Figure 2). The 3- and 5-year survival rates in the ablation and operation group were 66% and 78%, and 50% and 63%, respectively (Figure 3); however, there were no significant differences between groups. Child-Pugh B was significantly associated with poor disease-free and overall survival (Table 3). Multiple tumors were associated with overall survival. However, difference of treatment modality was not associated with prognosis in the present study. Table 4 shows 3-year survival rates in each score of mJIS; however, there were no significant

Table 2 Patient demographics between two groups in HCC patients

	Operation (*n* = 226)	Ablation (*n* = 52)	*P*-value
Age (yr)	60.2 ± 10.5	58.3 ± 10.7	0.074
Gender			
male/female	179/43	37/15	0.283
Time to treatment (yr)[1]	(5.1, 8.4, 11.2)	(5.4, 9.3, 11.6)	0.28
Background liver			
chronic hepatitis/cirrhosis/normal	119/94/13	4/48/0	< 0.001
Hepatitis virus			
B/C/B&C/non-B non-C	72/116/11/27	11/36/5/0	0.007
Child-Pugh classification			
A/B	201/25	34/18	< 0.001
Pretreatment			
Yes/No	78/148	0/52	< 0.001
Tumor size			
< 5 cm/ ⩾ 5 cm	160/66	49/3	< 0.001
Number of tumors			
solitary/multiple	174/52	37/15	0.479
Vascular involvement			
No/Yes	162/64	48/4	0.003
Adjuvant therapy			
Yes/No	5/221	0/52	0.615

[1]Each triplet gives the 25th, 50th and 75th sample percentiles. Time to the treatment since 1 January 1994.

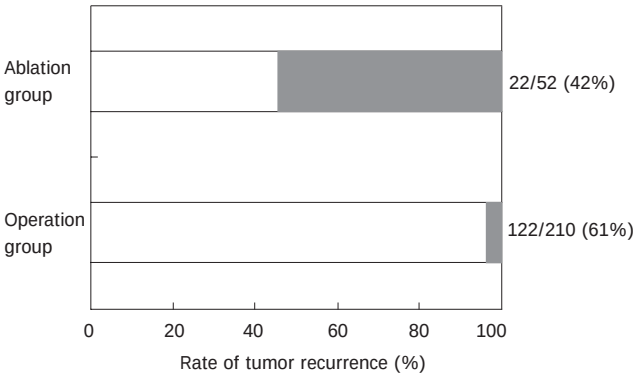

Figure 1 Tumor relapse and site of recurrence after treatment in two groups. Open square shows intrahepatic metastasis and closed square shows the local recurrence adjacent to treated lesion.

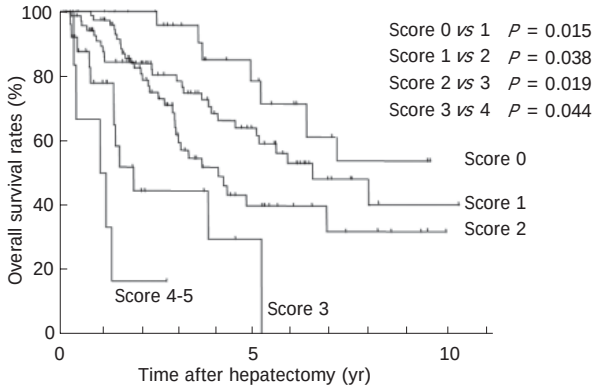

Figure 2 Survival using mJIS in HCC patients who underwent hepatic resection.

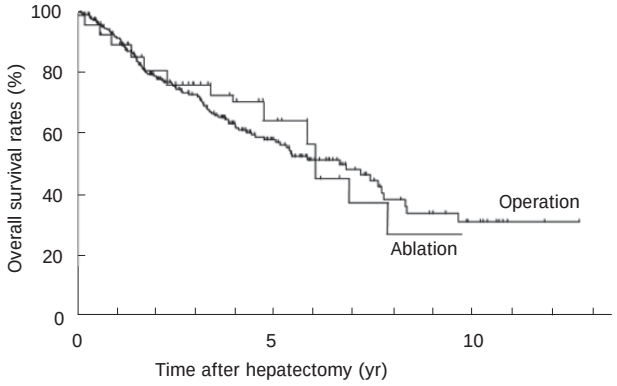

Figure 3 Comparison of survival in HCC patients between operation and ablation groups.

Table 3 Survival between two groups in HCC patients by multivariate analysis

	Disease-free survival		Overall survival	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Child-Pugh classification				
B *vs* A	2.05 (1.25-3.35)	0.004	2.46 (1.38-4.41)	0.002
Tumor size				
⩾ 5 *vs* < 5 cm	1.26 (0.83-1.92)	0.282	1.30 (0.75-2.25)	0.350
Macroscopic findings[1]				
Confluent type *vs* Simple nodular type	1.10 (0.75-1.61)	0.626	1.58 (0.92-2.72)	0.098
Number of tumor				
Multiple *vs* Solitary	1.23 (0.82-1.85)	0.306	1.73 (1.03-2.91)	0.037
Vascular involvement				
Yes *vs* No	1.24 (0.68-2.27)	0.481	1.76 (0.93-3.31)	0.080
Alpha-feto protein level				
⩾ 400 *vs* < 400 ng/mL	1.41 (0.93-2.11)	0.103	1.36 (0.81-2.28)	0.250
Treatment modality				
Ablation *vs* Hepatectomy	0.75 (0.46-1.22)	0.239	0.64 (0.39-1.34)	0.334

[1]Macroscopic findings defined by the *Classification of Primary Liver Cancer*[17].

Table 4 The 3-year survival rates in each score of mJIS after treatments in HCC patients

	Operation group (*n* = 226) (%)	Ablation group (*n* = 52) (%)
mJIS 0	96	98
mJIS 1	80	73
mJIS 2	66	70
mJIS 3	39	48
mJIS 4	35	28
mJIS 5	25	-

differences between the two groups. Overall survival rates between score 2 and 3 were remarkably different in both groups. Over 50% survival rates were obtained up to score 2 in both groups; however, survival rates over score 3 in both groups were lower.

DISCUSSION

With recent advances in the ablation technique, local tumor control has improved[25]. In comparison with alcohol injection, the modality option or patient survivals have been remarkably improved in the era of RFA or MCT[25-28]. Alcohol injection is not recommended at present[29,30]. In the present study, the ablation group included patients undergoing alcohol injection; however, local control was relatively good because of the small HCC in our series. At this stage, we mainly performed RFA regardless of tumor size, number and location and we also applied RFA under laparotomy or laparoscopy to achieve complete ablation. Selection bias for treatment was shown by our results. Hepatectomy was mainly selected in patients with chronic hepatitis or Child-Pugh A, while ablation was used in patients with impaired liver function such as cirrhosis or Child-Pugh B. In the latter, surgical resection is usually avoided. Concerning tumor factors, hepatectomy was preferably selected for tumors of larger size, and solitary and vascular involvement by the image examinations. Ablation tended to be selected for small and multiple tumors. Wakai *et al* also showed a similar tendency to select the treatment modality[31]. However, Shiina *et al* described the superiority of RFA compared to hepatectomy[32]. Therefore, superiority or selection criteria between both treatments are still controversial. In the recent Japanese guidelines for HCC, the indication of these treatments was not clearly discriminated[33]. In the operation group, other treatments were preferably performed in one-third of all patients. In these patients, ablation therapy was included as well. Based on these results, the background in both groups was remarkably different, which was also the case in Wakai's report[31].

The pattern of tumor relapse was different in the present study and local recurrence adjacent to the ablated section was significantly higher regardless of careful ablations with a sufficient ablation margin more than 5 mm[34]. Some investigators reported that the complete ablation rate is around 90% with HCC and less than 5 cm could be treated[27-29,35]. However, local recurrence in patients undergoing thermal ablation therapy ranged between 9.2% and 13.6%[26-28]. Hong *et al* reported that the local recurrence rate in ablation therapy was higher than that in hepatic resection[36]. Therefore, local control by hepatectomy is superior to that by thermal ablation at this stage, based on the above reports[26-28,31,35] and our results. Although the rate of distant liver metastasis might not be remarkably different based on previous reports[26-28,35,36], tumor recurrence in the distant liver was still high in the operation group in the present study, which might be

associated with the advanced stage of HCC as shown in the results.

With respect to patient survival after treatment, superiority between both groups was not clarified, in addition to survival rate, in our results. We applied the mJIS system in this study, which is the best available to predict HCC patient survival after curable treatments[9-11]. By applying this system, survival in each score in the present series was well discriminated. At this stage, indication of treatment modality in HCC patients with early tumor stage and Child-Pugh A or B between hepatectomy and thermal ablation has been controversial[31,32,34,37]. In patients with small HCC less than 2 cm or in patients with impaired liver function such as a Child-Pugh B, survival benefit was similar between both groups[31,34,37,38]. As described above, local recurrence rate by thermal ablation was higher compared to that by hepatectomy; however, overall survival was not significantly different by previous reports[26-28,34-37]. The guideline for diagnosis and treatment in HCC patients was first proposed by Makuuchi *et al*[33]; however, ablation and hepatectomy were at similar locations in HCC patients with less than four sites and good liver function. Our results showed that the overall survival was similar between both groups, which also had similar mJIS scores, although the included tumor factor and liver function were different between groups, as shown in patient demographics. By multivariate analysis, the difference of treatment modality was not observed in the present study. Up to mJIS score 2, the 3-year survival rate was well maintained; however, survival rate over mJIS score 3 was significantly decreased in both groups. We considered that this border between a score of 2 and 3 might be important to decide the limitation of both conventional treatments. The ultimate curable option should be a liver transplantation. Todo *et al* reported posttransplant survival in HCC patients who met Milan criteria undergoing living-related liver transplantation in Japan[14]. The 3-year survival rates with or without Milan criteria was 79% and 60%, respectively. This report was a satisfactory result at this stage. Compared to this result, even in a group with Milan criteria not met, survival rates over score 3 in both groups were lower than those in HCC patients undergoing living-related LT. In HCC patients with mJIS score 3-5, patients without remarkable vascular involvement would be included in the indication of liver transplantation. By comparing the survival benefit, transplantation is strongly recommended to improve patient prognosis. In patients with score 0-2, the definition of treatment criteria between groups seemed to be difficult on the present evidence and consensus[39,40]. A study with a large series in Japan will clarify this problem in the near future. Our results did not show superiority or definite indication between both treatment modalities in the present study. To improve the survival results in HCC patients, a combination of both treatments[41], chemoembolization[42], or intra-operative ablation under laparoscopy or laparotomy should be used[22,43].

In conclusion, hepatectomy tended to be selected in patients with better functional liver reserve and, hence, ablation therapy tended to be selected in patients with poor hepatic function in our series. In the ablation group, local recurrence near the treatment region tended to be more than that in the hepatectomy group. By multivariate analysis, macroscopic finding and vascular invasion were significant risk factors, but treatment modality was not a prognostic factor. According to the mJIS system, both treatments could be selected for patients with score 0-2; however, for patients with a score more than 3, liver transplantation might be a better option compared to conventional local treatments.

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