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A Comparison of Hepatic Resection and Ablative Therapy regarding the Survival of Hepatocellular Carcinoma Patients in Nagasaki

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To identify the effect of local treatments for hepatocellular carcinoma (HCC) in our associated institutes in Nagasaki prefecture, we performed a comparative study of hepatic resection and local ablative therapies, including alcohol injection, microwave coagulation and radio-frequency ablation. We examined the patient demographics, outcomes and tumor-free and overall survival between a hepatectomy group (n=210) and a local ablative therapy group (n=52). In the ablative therapy group, there were significantly more patients with cirrhosis and poorer hepatic function than in the hepatectomy group ($p<0.001$). Larger tumors and vascular involvement in the hepatectomy group were significantly more frequent than in the ablative therapy group ($p<0.001$ and $p=0.002$, respectively). The multivariate Cox regression analysis indicated no significant difference either in the time to the first recurrence of tumor after surgery or in mortality between ablative therapy and hepatectomy. By making full use of various modalities in each specialty, the satisfactory HCC treatment could be achieved at this stage.

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Introduction

Hepatic resection has been thought the best option for radical treatment of hepatocellular carcinoma (HCC).[1-7] However, in injured liver diseases, candidates for hepatectomy must have good hepatic functional reserve.[4,6] In the last decade, other local treatment modalities such as alcohol injection, microwave coagulation (MC), cryoablation and radio-frequency ablation (RFA) have been developed for HCC treatment when surgical resection is contraindicated due to poorer hepatic function because such modalities require minimal invasion.[3,4,6] Although local ablative therapy has been widely applied, it is limited to smaller HCC.[6-9] Furthermore, treatment effectiveness is evaluated only by X-ray or needle biopsy, and tumor recurrence in ablated lesions is not rare.[10-12] Studies of the prognosis of HCC patients comparing hepatectomy with alcohol injection have been reported previously, and patient survival after hepatectomy may be superior to alcohol injection.[1,7,13] However, the clinical effectiveness of hepatectomy and other local modalities is still controversial.[4,6,8,11,14]

Recently, an attempt was made to formulate guidelines for HCC treatment in the Japanese series according to reliable evidence, which was proposed at the conference "Digestive Diseases Week (DDW)-Japan 2003" held in Osaka in October 2003 (not published). In this study, we conducted a retrospective analysis of prognosis in 262 Japanese HCC patients after hepatic resection or ablation therapy in several hospitals in Nagasaki prefecture. To identify the effect of local treatments for HCC, we made a comparative study of patient demographics, outcomes and survival between hepatic resection and local ablative therapies, including alcohol injection, MC and RFA.

Patients and Methods

Patients

Data were collected during surgery from 262 patients with HCC who were admitted to the Division of Surgical Oncology (Takeshi Nagayasu M.D., Professor and Chairman) and the Second Department of Internal Medicine (Shigeru Kohno M.D., Professor and Chairman),

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Nagasaki University Graduate School of Biomedical Sciences, and its associated hospitals (Sasebo Chuo Hospital, Nagasaki Atomic Bomb Disease Hospital, Sasebo Municipal Hospital and Mitsubishi Hospital) between January 1990 and September 2003.

Demographics of patients who underwent hepatic resection and ablative therapy

Prior to surgery for HCC, 72 of 210 patients who underwent hepatectomy, were treated with either chemoembolization (n=65), alcohol injection (n=3) or received a combination of these two modalities (n=4). The operative procedures included lobectomy or extended lobectomy (n=56), segmentectomy or subsegmentectomy (n=70) and partial resection (n=84). Radical hepatectomy was performed to remove the hepatic tumor, leaving no residual tumor. All hepatic tumors were completely resected without macroscopic exposure of the remaining liver to the amputated section. After surgery, 4 patients (1.9%) received adjuvant 5-fluorouracil chemotherapy by intra-arterial injection through a subcutaneously implanted reservoir to prevent tumor recurrence. The minimum follow-up period after hepatic resection of HCC was 12 months. Seven of 125 (5.6%) patients who survived were lost to follow-up and we treated them as censored on the last date that they were known to be alive.

Of 52 patients who underwent ablation therapy, 15 were treated with alcohol injection (29%), 32 received RFA (62%) and 5 received MC (9%). Tumor recurrence in 22 patients (42%) after ablation therapy occurred near the ablated area (n=17) and in other areas (n=5) in the liver. All hepatic tumors were completely ablated with a 5-10 mm safety margin detected by computed tomography. The minimum follow-up period after ablation of HCC was 9 months.

The study design was approved by the Ethics Review Board of Nagasaki University Graduate School of Biomedical Sciences, and written informed consent for treatment was obtained from each patient.

Assessment of each factor was confirmed by histopathological examination of the resected specimen, or by computed tomography scan, ultrasonography, magnet resonance imaging or angiography. We used the tumor node metastasis (TNM) classification system of the Liver Cancer Study Group of Japan (Table 1)[15] and the Japan Integrated Staging (JIS) score defined as the sum of the two scores corresponding to Japanese TNM classification and Child-Pugh classification as shown in (Table 2).[16]

Distribution of age and time to treatment was compared between hepatectomy and ablative therapy groups by the Wilcoxon rank-sum test, while nominal scale data such as gender and ordinal scale data such as dichotomized tumor size were compared between the two groups by the chi-square test. The time to the first recurrence of tumor after surgery and the mortality were compared between hepatectomy and ablative therapy groups by the log-rank test. The effects of prognostic factors on the time to the first recurrence of tumor after surgery and the mortality were analyzed using the proportional hazards model. Necessary calculations were performed using the statistical software of STATISTICA™ (Stat Soft, Tulsa, OK).

Table 1. Definition and criteria of the TNM stage for HCC by the Liver Cancer Study Group of Japan[15]

Factors	
1) Number of tumors: single	
2) Tumor size: < 2 cm	
3) No vessel invasion (portal vein, hepatic vein, bile duct)	
T1	Fulfilling all three factors
T2	Fulfilling two factors
T3	Fulfilling one factor
T4	Fulfilling none of the factors
N	Regional
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0
Stage IV-A	T4 N0 M0 or T1-T4, N1 M0
Stage IV-B	T1-4, N0 or 1, M1

Table 2. Definition and criteria of the JIS score[16]

	Score			
	0	1	2	3
Japanese TNM stage	I	II	III	IV
Child-Pugh's classification	A	B	C	

Results

Demographic and other background features of HCC patients in the hepatectomy and ablative therapy groups are shown in Table 3. Though not significant (p=0.064), patients in the ablative therapy group were on the average older than those in the hepatectomy group. No significant difference was observed between the two groups in the time to treatment from the commencement of the study. In the ablative therapy group, there were significantly (p<0.001) more patients with cirrhosis and poorer hepatic function than in the hepatectomy group. Furthermore, in the ablative therapy group, there were significantly (p=0.001) more patients with higher JIS score than in the hepatectomy group. Non-B, non-C patients were not observed in the ablative therapy group. Larger tumors and vascular involvement were significantly more frequent (p<0.001 and p=0.002, respectively) in the hepatectomy group than in the ablative therapy group. No patients in the ablaptive therapy group received either pretreatment or adjuvant treatment.

Child-Pugh's classification and JIS score showed a significant association with the time to the first recurrence of tumor after surgery (p=0.004 and p=0.014, respectively, as well as with the mortality (p=0.002 and p=0.045, respectively) (Table 4). In the hepatectomy group, 132 (62.9%) recurred tumor and 90 (42.9%) died, while in

the ablative therapy group, 22 (42.3%) recurred tumor and 15 (28.8%) died. However, no significant difference was observed in the time to the first recurrence of tumor or in mortality between ablative therapy and hepatectomy (Table 4). Furthermore, no significant difference was observed in the time to the first recurrence of tumor or mortality by JIS score between the hepatectomy and ablative therapy groups (Figures 1 and 2).

Table 3. Comparison of the demographic and background features between HCC patients who received hepatectomy and ablative therapy

Factor	Hepatectomy (n=210)	Ablative therapy (n=52)	*p*-value
Age (years)	(59, 64, 71)[a] 23-81[b]	(61, 69, 72)[a] 39-79[b]	0.064
Time to treatment (years)[c]	(5.1, 8.4, 11.2)[a] 0.04-12.84[b]	(5.4, 9.3, 11.6)[a] 0.57-12.86[b]	0.280
Gender Male/Female	170/40	37/15	0.173
Background liver disease[d] CVH/LC/HF/NL	111/87/5/7	4/48/0/0	<0.001
Virus causing hepatitis B/C/B&C/non-B non-C	66/108/10/26	11/36/5/0	0.007
Child-Pugh classification A/B, C	188/ 22	34/ 18	<0.001
Pretreatment Yes/No	77/133	0/52	<0.001
Tumor size <5cm/≥5cm	145/65	49/3	<0.001
Number of tumors Solitary/Multiple	162/48	37/15	0.469
Vascular involvement of tumor Yes/No	151/ 59	48/ 4	0.002
JIS score 0-2/3-4	178/32	33/19	0.001
Adjuvant chemotherapy Yes/ No	4/206	0/52	0.588

[a]Each triplet gives the 25th, 50th and 75th sample percentiles.
[b]Minimum-Maximum.
[c]Time to the treatment since 1 January 1990.
[d]CVH = chronic viral hepatitis; LC = liver cirrhosis; HF = hepatic fibrosis; NL = normal liver.

Table 4. Effects of prognostic factors on the time to the first recurrence of tumor and the time to death after surgery in HCC patients

Factor	Time to the first recurrence of tumor after surgery		Time to death after surgery	
	HR (95% CI)[a]	*p*-value	HR (95% CI)[a]	*p*-value
Child's classification B, C 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[b] SNEG, CMV vs. SN	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
AFP ≥400 vs. <400 ng/ml	1.41 (0.93-2.11)	0.103	1.36 (0.81-2.28)	0.250
JIS score ≥3 vs. 0-2	2.10 (1.16-3.79)	0.014	1.95 (1.02-3.76)	0.045
Modality Ablation vs. hepatectomy	0.75 (0.46-1.22)	0.239	0.64 (0.39-1.34)	0.334

[a]Hazrd ratio (HR) estimated by the proportional hazards model with 95% confidence interval (CI) in parentheses.
[b]Types of HCC: SN = single nodular; SNEG = single nodular with extranodular growth; CMN = confluent multinodular.

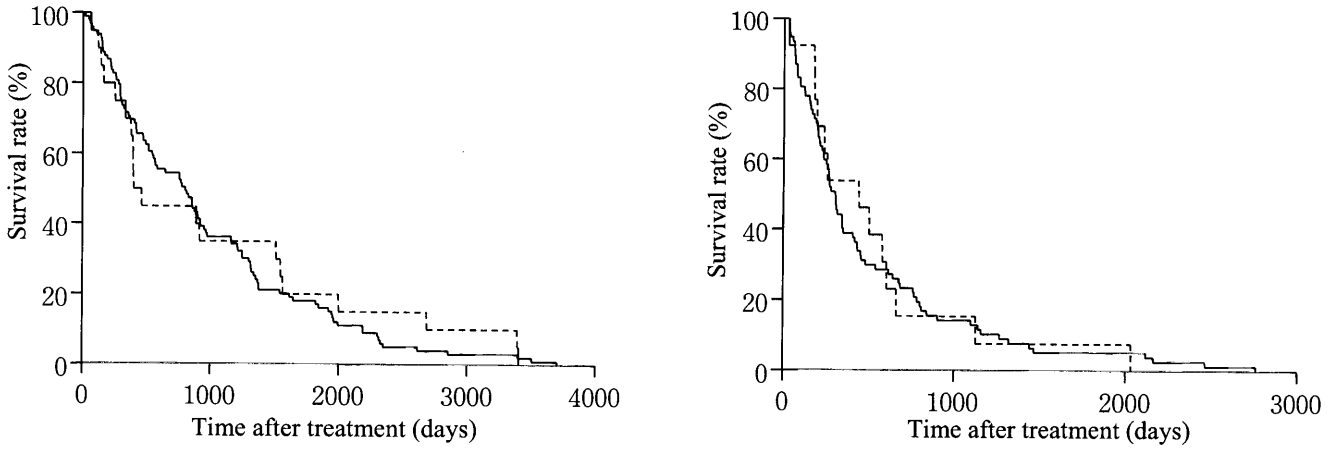

Figure 1. Kaplan-Meier survival function estimates for the time to the first recurrence of tumor after treatment in patients with HCC who received hepatectomy (solid line) and ablation therapy (dotted line). The upper and lower panels depict the Kaplan-Meier survival function estimates for 143 HCC patients with JIS score 0-1 (114-hepatectomy and 29-ablative therapy) and 119 HCC patients with JIS score 2-4 (96-hepatectomy and 23-ablative therapy), respectively. No significant difference in the survival function was observed between the two groups of treatment for either patients with JIS score 0-1 (p=0.738) or those with JIS score 2-4 (p=0.961).

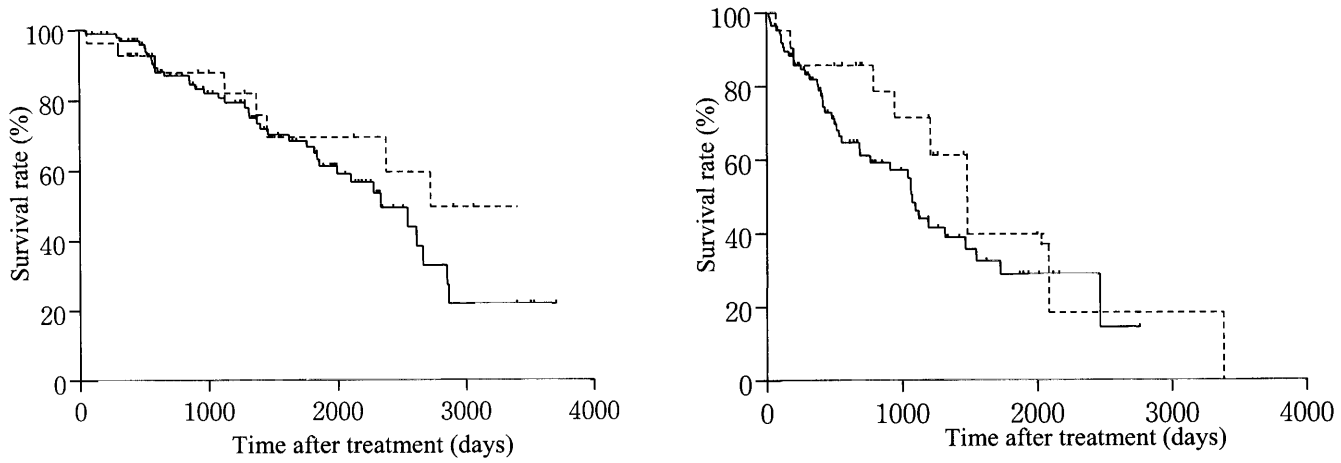

Figure 2. Kaplan-Meier survival function estimates for the time to death after treatment in patients with HCC who received hepatectomy (solid line) and ablation therapy (dotted line). The upper and lower panels depict the Kaplan-Meier survival function estimates for 143 HCC patients with JIS score 0-1 (114-hepatectomy and 29-ablative therapy) and 119 HCC patients with JIS score 2-4 (96-hepatectomy and 23-ablative therapy), respectively. No significant difference in the survival function was observed between the two groups of treatment for either patients with JIS score 0-1 (p=0.376) or those with JIS score 2-4 (p=0.398).

Discussion

Ablative therapy, particularly MC and RFA, has become a useful treatment modality to control HCC, even in patients with poorer hepatic function.[4,8,11,12,17] These modalities are also useful for tumor control while awaiting liver transplantation.[6,12] In this study, ablative therapy was also applied for patients with liver cirrhosis or poorer hepatic function, for whom hepatectomy was contraindicated, to compare with the hepatectomy group. Ablative therapy is useful for such high risk patients because it is less invasive and repeated treatment is possible.[6,10-12] In the hepatectomy group, one third of patients had pretreatment such as chemoembolization or ablation therapy in this study. The planned pretreatment was performed in a couple of cases according to the policy of the physicians. However, most tumors were not fully controlled by the initial treatment in our series. Local treatment or chemoembolization should be selected as the first option in smaller and non-infiltrative HCC.[3,4,6-9,11] We have sometimes noted that such modalities continued too long, nevertheless tumor growth and invasion were not controlled by any local treatments. In such cases, we stress that the protocol must be changed immediately and surgical treatment should be considered by careful observations. Down-staging for advanced HCC by ablation or chemoembolization before hepatectomy may be useful.[18]

Complete ablation in larger HCC using ablation therapy was difficult.[11] On the other hand, ablative therapy was more available for multiple tumors in both lobes of the liver because of reduced invasiveness.[6,11,19] In this study, ablative therapy was used for smaller HCC rather than hepatectomy, and for multiple HCC as well as hepatectomy. Alcohol injection or RFA has been applied for patients with 2 or 3 tumor lesions of size not exceeding 3 cm,[6,9] or for patients with one tumor lesion of size not exceeding 5 cm,[8] and this indication may increase. Hepatectomy was applied for HCC with vascular involvement due to the difficulty of complete control by ablation, and a sufficient safety margin cannot be obtained because of the cooling effect in such cases.[21] These results indicated that hepatectomy should be selected in more advanced or invasive HCC compared to ablation therapy.

In this study, tumor recurrence such as intrahepatic distant metastasis or multicentric carcinogenesis after hepatectomy was similar to that after ablative therapy. However, local recurrence near the transected edge of the liver was observed in only five of 128 patients (3.9%). On the other hand, 17 of 22 patients had obvious local recurrence near or in the ablated area. The local recurrence rate after alcohol injection, MC and RFA was 18-41%,[22-24] 6-11%[22,25,26] and 4-30%,[10,25,27,28] respectively. These recurrence rates were not low and, therefore, physicians must be aware that a non-enhanced low density area after ablation therapy detected by X-ray is not necessarily complete necrosis and careful observation should be necessary. Horigome et al. reported that most recurrence after alcohol injection or MC was intrahepatic metastasis although multicentric occurrence was predominant in recurrences after hepatectomy.[29]

In recurrent patients after hepatectomy, chemoembolization was often applied because of worsened hepatic function, multiple recurrence, and insufficient hepatic volume for repeated resection. Repeated resection or ablation has been used for recurrent HCC of limited number and smaller size.[30,31] Coagulation therapy has recently been applied in such recurrent HCC after hepatectomy due to its reduced invasiveness compared to surgical resection. Matsuda et al. reported that ablative therapy was a good option to control tumor recurrence after hepatic resection.[31] In the ablative therapy group, repeated treatment was feasible in half of the recurrent patients.

In previous reports, partial hepatectomy and liver transplantation provided the best curative therapy and showed better survival in HCC patients.[1,2] However, the difference of survival between hepatectomy and alcohol injection in the early stage of HCC was controversial.[1,4,9,14] Although local control of microwave coagulation or RFA was superior

to that of alcohol injection,[8,22] no long-term comparative analysis between hepatectomy and ablative therapy has been fully reported at this stage. Furthermore, the superiority of these treatment modalities concerning survival benefit using multivariate analysis has not been assessed, to our knowledge. In this study, no significant difference was observed between hepatectomy and ablative therapy with respect to either the time to the first recurrence of HCC or mortality. In addition, no significant difference was observed in the time to the first recurrence of tumor or mortality by JIS score between the two groups. Although we cannot reach a complete conclusion at this stage because of probable biases in the assignment of the patients to the two treatment groups, we consider that satisfactory HCC treatment can be achieved by making full use of the various modalities and following a careful treatment protocol from each specialist physician. The DDW-Japan 2003 has discussed the establishment of guidelines for HCC treatment and has proposed that therapy for HCC should be decided from hepatic functional reserve and tumor-related factors (not published yet). Trials following standardized guidelines are necessary for physicians, radiologists and surgeons who are engaged in HCC treatment in Japan.

Conclusion

Hepatectomy and local ablative therapy groups of HCC patients were analyzed by collecting data in Nagasaki prefecture. Hepatectomy tended to be selected for advanced tumors and patients with better hepatic functions whereas ablative therapy tended to be selected for smaller HCC and patients with poorer hepatic function. The risk of tumor recurrence and overall survival after treatment was not significantly different between the hepatectomy and local ablative therapy groups by multivariate analysis. We conclude that satisfactory HCC treatment can currently be achieved by the full use of various modalities by liver physicians and surgeons. Further investigations and long-term analysis are necessary to ascertain the superiority of modalities in HCC.

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