comparison with their sporadic MSI-H counterparts.[35] Controversy remains regarding the use of microsatellite instability for predicting the prognosis or benefit of 5-fluorouracil-based chemotherapy in patients.

Microsatellite instability (MSI) is a consequence of the inactivation of a mismatch repair gene and is observed in approximately 10–30% of gastric cancer cases. The clinical significance of high levels of MSI (MSI-H) in gastric cancer has been reported.[12,28,31,33,34,36] The purpose of this study was to investigate the prognostic significance of high levels of MSI (MSI-H) in gastric cancer patients, and to investigate the predictive significance in relation to 5-fluorouracil-based chemotherapy. Tumors resected from 240 patients with sporadic gastric cancer were examined using a unique fluorescent technique, high-resolution fluorescent microsatellite analysis (HRFMA), to determine the frequencies of the MSI (MSI-H) in gastric cancer.[31,32] In this system, several devices were prepared to improve reproducibility of the polymerase chain reaction products, migration accuracy of electrophoresis, and characteristics of the detection system. HRFMA provides precise and objective analyses of microsatellite alterations.[31,33] In previous reports, gastric cancer with MSI-H had a significantly higher frequency of antral location and intestinal subtype, but a lower incidence of lymph node metastasis in comparison with gastric cancer with MSI-L or MSS.[1,7,37,38] The MSI-H gastric cancers in the current study were also significantly associated with older age and antral location, but not intestinal subtype. Gastric cancers with and without high-frequency microsatellite instability (MSI-H) represent distinctive pathways of carcinogenesis.[39] A high frequency of MSI was reported in intestinal metaplasia and this suggests that intestinal metaplasia and well-differentiated adenocarcinoma in the stomach may have the same molecular backgrounds.[37] In the analysis of Japanese patients, the high incidence of the diffuse type of gastric cancer may result in the low frequency of MSI-H. As a result, the significant association between MSI-H and intestinal-type cancer might not be clearly proven. In the current analysis, MSI-H was not significant but slightly more frequently found in the intestinal type of gastric cancer than in the diffuse type of cancer. Moreover, previous reports considered the low frequency of lymph node metastasis to be a reason for good prognosis of MSI-H patients. However, the occurrence of lymph node metastasis is not so infrequent in MSI-H tumors, and a rather large degree of lymph vessel invasion was also observed in our cases. These phenomena may therefore have affected the results regarding the prognosis.

The current analysis showed no clear influence of MSI status on overall survival. All of the patients in the current study underwent a D2 lymphadenectomy according to the Japanese Guidelines for Diagnosis and Treatment for Carcinoma of Stomach, and the prognosis was better than that described in a previous report, in spite of the high rate of lymph node metastasis. Even if there are lymph node metastases or lymph vessel involvement in MSI-H patients, a D2 lymphadenectomy may overcome the negative impact of the prognosis for the lymph node metastasis. Accordingly, no difference was found in the prognosis between MSI-H and MSI-L/N tumors. At least, MSI cannot be regarded as a prognostic factor in our results.

Multimodal treatment protocols are increasingly employed to improve the survival of patients with locally advanced adenocarcinomas of the upper gastrointestinal tract; however, only 30–40% of patients respond to 5-FU and cisplatin-based neoadjuvant chemotherapy.[40] Recently, S-1, an oral derivative of 5-fluorouracil, has proven to be an effective adjuvant treatment for East Asian patients who have undergone a D2 dissection for locally advanced gastric cancer.[23,41] Adjuvant chemotherapy was done on advanced-stage cancer and the patients treated with adjuvant chemotherapy showed poorer prognosis (Fig. 2a). Many studies have evaluated the role of high levels of microsatellite instability (MSI) as a predictor of the response to chemotherapy in colorectal cancer. Adjuvant chemotherapy improves the overall survival among patients with microsatellite-stable tumors or tumors exhibiting low-frequency microsatellite instability.[25] In the current gastric cancer cases, MSI-H phenotype did not predict any benefit of adjuvant chemotherapy on overall survival (OS). However, no difference could be detected in our study since adjuvant chemotherapy had only been administered to 76 cases. Therefore, sensitivity to 5-FU was investigated with an MTT assay using tissue samples. The assay showed that MSI phenotype has no correlation with chemosensitivity in an in vitro sensitivity test. Therefore MSI phenotype was not a predictive factor for adjuvant chemotherapy of gastric cancer.

In conclusion, in a series of 240 patients with gastric cancer, MSI-H did not demonstrate any particular benefit as either a prognostic factor or a predictive factor for the response to chemotherapy in comparison with patients with MSS/MSI-L tumors. Due to the conflicting results of the available data and the lack of any prospectively performed randomized studies, it is therefore considered to be premature to use MSI status routinely to determine optimal individual patient management in gastric cancer cases.

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ORIGINAL ARTICLE – HEPATOBILIARY AND PANCREATIC TUMORS

Both Fibrous Capsule Formation and Extracapsular Penetration Are Powerful Predictors of Poor Survival in Human Hepatocellular Carcinoma: A Histological Assessment of 365 Patients in Japan

Tomohiro Iguchi, MD[1], Shinichi Aishima, PhD[1], Kensaku Sanefuji, MD[2], Nobuhiro Fujita, MD[1], Keishi Sugimachi, PhD[2], Tomonobu Gion, PhD[2], Akinobu Taketomi, PhD[2], Ken Shirabe, PhD[3], Yoshihiko Maehara, PhD[2], and Masazumi Tsuneyoshi, PhD[1]

[1]Department of Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan;
[2]Department of Surgery and Sciences, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan;
[3]Department of Surgery, Iiduka Hospital, Fukuoka, Japan

ABSTRACT

Background. A new definition of infiltration to the capsule (fc-inf) has been proposed as a novel marker for predicting the prognosis of 88 patients with hepatocellular carcinoma (HCC). The current aim was to present evidence to develop the fibrous capsule and fc-inf, from the Japanese histological findings for HCC, and to validate their biological significances and predictive power of survival in a large series.

Methods. A total of 365 HCCs were divided into HCCs without the fibrous capsule (NC type; $n = 135$) and HCCs with the fibrous capsule (FC type; $n = 230$). Then, FC type was subclassified into two types: extracapsular infiltrating (EC) type ($n = 125$), in which cancer cells penetrated outside the fibrous capsule, and intracapsular (IC) type ($n = 105$), in which the infiltrating cancer cells stayed inside the fibrous capsule.

Results. The proportion of less histological differentiation and portal venous invasion was higher in FC type than in NC type. The fibrous capsule came to be observed according to the increase of tumor size ($P < 0.0001$). FC type had significantly poorer outcome for overall survival than NC type ($P = 0.0022$). EC type showed more intrahepatic metastasis than IC type. The macroscopic subclassifications were significantly affected the presence of fc-inf. EC type had significantly poorer outcome for disease-free survival than IC type ($P = 0.0132$) and was an independent prognostic factor for disease-free survival ($P = 0.0482$).

Conclusions. Fc-inf defined as extracapsular penetration was verified to be a novel marker for predicting prognosis, and presence of fc-inf might be predicted by tumor gross features.

Hepatocellular carcinoma (HCC) is the fifth most common neoplasm in the world, and its incidence is increasing in the USA and Europe.[1–5]

A pathological investigation of HCC has been performed in Japan. Because HCC has a high incidence of recurrence after hepatic resection or other locoregional therapy and therapeutic options for HCC vary, it is important to evaluate resected HCCs histologically.[6–8]

The definition of the fibrous capsule and infiltration to the fibrous capsule (fc-inf), which are unique characteristics of HCC, still remains unsatisfactory and pathologists have not yet evaluated these factors in a unified way.

Previously, 88 patients with encapsulated HCC, measuring ≤5 cm in diameter, were evaluated together with the single nodular and single nodular with extranodular growth type, and a new definition of fc-inf was proposed as a novel marker for predicting patient prognosis.[9]

The current study was designed to validate the new definition of fc-inf in a large series, including HCCs without complete fibrous capsule, measuring >5 cm in diameter, or with the confluent multinodular type.

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T. Iguchi, MD
e-mail: tomo@surgpath.med.kyushu-u.ac.jp

MATERIALS AND METHODS

Patients

Between September 1985 and December 2004, 863 patients underwent hepatectomy and were diagnosed to have HCC at Kyushu University Hospital (Fukuoka, Japan). Any cases with preceding therapy and a noncurative operation were excluded. The macroscopic typing of HCC, which was advocated by the Liver Cancer Study Group in Japan, included the nodular, massive, diffuse, and unclassified types.[10] The nodular type could be additionally subclassified into four types: small nodular type with indistinct margin, single nodular, single nodular with extranodular growth type, and confluent multinodular.[10,11] The HCCs of nodular type, excluding the massive, diffuse, and unclassified types, were evaluated. Most of these included the cases with noncurative operations, that had no complete fibrous capsule, or in which the evaluation of fibrous capsule was too difficult. As a result, 365 patients, including 88 patients from the previous study, were evaluated.[9]

The mean number of follow-up days after the initial hepatic resection was 1,609.2 ± 1,102.4 days (range 14–4,959 days). Any postoperative survival or recurrence was entered into the database immediately when a patient either died due to HCC or a recurrence was strongly suspected. Two hundred and fifty-seven of the 365 patients experienced a recurrence of disease in 1.4 years, and 116 patients had died in 3.4 years, the median period after hepatic resection. Informed consent was obtained from each patient included in the study.

Ages of the patients ranged from 28 to 83 years, with an average of 63.0 years. The male-to-female ratio was 288:77. Two hundred and twenty-five patients (61.6%) had hepatitis C virus antibody (HCV-Ab) alone, 61 patients (16.7%) had hepatitis B virus surface antigen (HBs-Ag) alone, 75 patients (20.5%) had neither HCV-Ab nor HBs-Ag, and 14 patients (3.8%) had both HCV-Ab and HBs-Ag. The clinicopathological variables were defined according to the *General Rules for the Clinical and Pathological Study of Primary Liver Cancer* of the Liver Cancer Study Group of Japan.[10] Macroscopically, HCCs were subclassified as single nodular type ($n = 254$) including small nodular type with indistinct margin ($n = 31$), single nodular with extranodular growth type ($n = 64$), and confluent multinodular type ($n = 47$). The mean ± standard deviation and the median of the tumor size were 3.84 ± 2.77 cm and 3.00 cm, respectively. All tumors were histologically diagnosed as well-differentiated HCC ($n = 39$), moderately differentiated HCC ($n = 223$) or poorly differentiated HCC ($n = 103$). Presence of septal formation, serosal infiltration, portal venous invasion, hepatic venous invasion, bile duct invasion, and intrahepatic metastasis was observed in 248 (67.9%), 163 (44.7%), 146 (40.0%), 62 (17.0%), 22 (6.0%), and 102 (27.9%) cases, respectively. The noncancerous liver tissue specimens showed cirrhosis in 166 (41.8%) cases. All specimens were fixed in 10% formalin, embedded in paraffin, cut into 3-μm sections, and stained by hematoxylin–eosin.

Classification of the Fibrous Capsule and Capsular Infiltration

One hundred and thirty-five HCCs had no complete fibrous capsule, regarded as the noncapsular (NC) type (Fig. 1). Two hundred and thirty HCCs surrounded by the fibrous capsule, the fibrous capsular (FC) type (Fig. 1), were classified into two subgroups: infiltrating pattern into extracapsular infiltrating type (EC type, $n = 125$), in which the infiltrating cancer cells were present outside the fibrous capsule and touched the existing liver parenchyma, and intracapsular type (IC type, $n = 105$), in which the infiltrating cancer cells were present inside the fibrous capsule and lacked a connection with the existing liver parenchyma.[9]

Statistical Analysis

Comparison between each type and the clinicopathological findings was evaluated using χ^2-test, Student's t test, and Mann–Whitney's U-test. Akaike's information criterion (AIC) was used to evaluate the fit of the logistic regression models, predicting whether EC or IC type was subclassified from the parameters. Patient survival analysis was calculated by Kaplan–Meier method and differences were evaluated by the log-rank test. The factors of the metric variables suspected the assumption of the linear risk were divided by the median points and a Cox proportional hazards model was used in the multivariate survival analysis. The infiltrating type (EC versus IC type) and all evaluated clinicopathological findings were added to the multivariate analysis. These results were analyzed using the StatView-J 5.0 software program (SAS Institute Inc., NC, USA, 1992–1998). P values less than 0.05 were considered statistically significant.

RESULTS

Clinicopathological and Prognostic Comparisons Between the Noncapsular Type and the Fibrous Capsular Type

The noncapsular (NC) type was observed in 135 cases (37.0%) and the fibrous capsular (FC) type was observed in

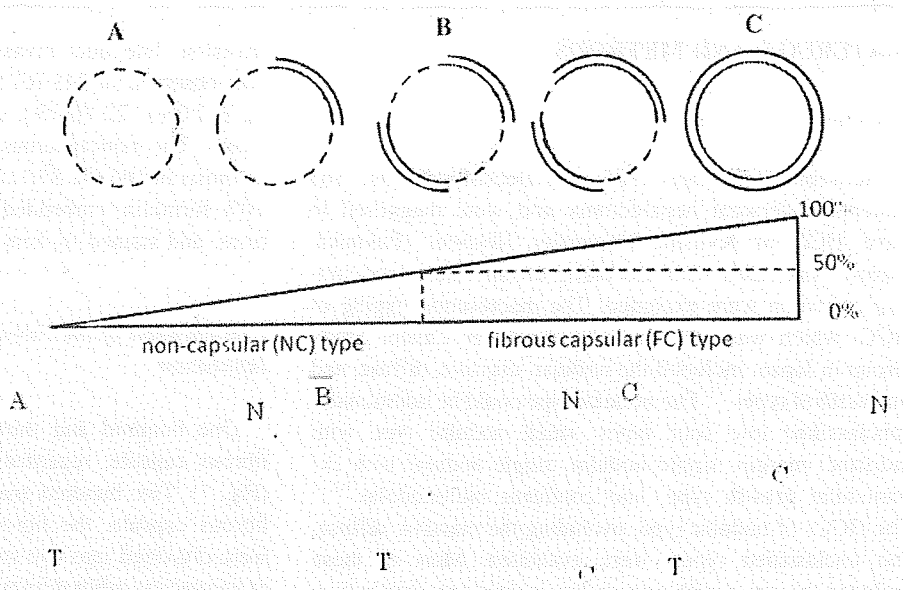

FIG. 1 Degree of coverage by the fibrous capsule in hepatocellular carcinoma (HCC): more than 50%, fibrous capsular (FC) type; less than 50%, noncapsular (NC) type. Representative schematic drawing (*top*) and hematoxylin–eosin stain (*bottom*). (a) HCC without any fibrous capsule, NC type, (b) 50% of HCC covered with the fibrous capsule, defined as FC type, (c) HCC completely covered with the fibrous capsule. Original magnification: ×40 (a–c). *Solid line* histologically defined fibrous capsule, *dotted line* histologically undetected fibrous capsule, *shaded area* cancerous tissue, *T* main tumor, *N* noncancerous tissue, *C* fibrous capsule

230 cases (63.0%; Table 1). The FC type had only one case showing well-differentiated HCC, while the NC type had 38 cases showing well-differentiated HCC. More major surgical procedures were performed for FC type than for NC type, and FC type showed more blood loss and wider surgical margins than NC type. FC type characteristically represented single nodular with extranodular growth type or confluent multinodular type, showed less-differentiated histology, higher septal formation, serosal infiltration, and portal venous invasion, and worse Edmondson classification than NC type. Thirty-one patients with small nodular type with indistinct margin were subclassified into 30 cases of NC type and 1 case of FC type (data not shown).

The percentage of the FC type in ≤2, 2–3, 3–5, and >5 cm lesions was 31.3% ($n = 26$), 58.4% ($n = 59$), 78.9% ($n = 90$), and 82.1% ($n = 55$), respectively (Fig. 2). The fibrous capsule came to be observed as the tumor grew when referred in each tumor diameter ($P < 0.0001$).

Analysis of disease-free and overall survival revealed that patients with FC type had poorer outcomes than those with NC type ($P = 0.0878$ and $P = 0.0022$, respectively; Fig. 3). However, FC type was not an independent prognostic factor for disease-free or overall survival ($P = 0.0510$ and $P = 0.0529$; data not shown).

Clinicopathological Comparisons Between the Extracapsular Infiltrating Type and the Intracapsular Type

The intracapsular (IC) type was observed in 105 cases (45.7%) and the extracapsular infiltrating (EC) type was observed in 125 cases (54.3%; Table 2). Indocyanine green retention rate at 15 min (ICG_{15}) had a lower value and more major surgical procedures were performed for EC type in comparison with IC type. EC type also characteristically represented single nodular with extranodular growth type or confluent multinodular type, and showed higher intrahepatic metastasis and worse Edmondson classification than IC type.

The percentage of EC type in FC type, in ≤2, 2–3, 3–5, and >5 cm tumors was 38.5% ($n = 10$), 45.8% ($n = 27$), 55.6% ($n = 50$), and 69.1% ($n = 38$), respectively (Fig. 4). Infiltration to the fibrous capsule was observed as the tumor grew when referred in each tumor diameter ($P = 0.0242$).

In addition, the macroscopic single nodular with extranodular growth type and confluent multinodular type significantly affected the presence of fc-inf in comparison with macroscopic single nodular type, according to logistic regression analysis ($P = 0.0185$ and $P = 0.0090$, respectively).

Outcome After Surgery and Prognostic Factors Between the Extracapsular Infiltrating Type and the Intracapsular Type

The disease-free survival rate for IC type at 1, 3, and 5 years was 71.0%, 48.0%, and 25.5%, and that for EC type at 1, 3, and 5 years was 67.0%, 27.2%, and 18.4%, respectively (Fig. 5a). Analysis of disease-free survival also revealed that patients with EC type had significantly poorer outcomes than those with IC type ($P = 0.0132$). In addition, overall survival rate for IC type at 1, 3, and

TABLE 1 Comparative analysis of clinicopathological findings between fibrous capsular (FC) type and noncapsular (NC) type

	NC type (n = 135)	FC type (n = 230)	P value
Clinical factors			
Age (years)	62.4 (8.7)[a]	63.4 (8.5)[a]	0.2986
Sex (male/female)	104/31	184/46	0.5092
Viral infection			
HBs-Ag (+) (%)	17.0	22.7	0.2278
HCV-Ab (+) (%)	69.6	63.0	0.2117
Albumin (g/dl)	3.9 (0.4)[a]	3.8 (0.4)[a]	0.3877
ALP (U/L)	254 (197, 314)[b]	251 (179, 326)[b]	0.4061
Total bilirubin (mg/dl)	0.8 (0.6, 1.0)[b]	0.8 (0.6, 1.0)[b]	0.3534
AST (IU/L)	55 (36, 79)[b]	53 (36, 79)[b]	0.9668
ALT (IU/L)	56 (34, 96)[b]	59 (34, 91)[b]	0.8319
Platelet ($\times 10^4/\mu L$)	11.4 (9.1, 15.7)[b]	13.1 (9.6, 16.4)[b]	0.2123
Prothrombin time (s)	85 (75, 99)[b]	90 (80, 100)[b]	0.0606
ICG_{15} (%)	15.8 (10.7, 24.2)[b]	14.4 (9.8, 20.4)[b]	0.8537
AFP (ng/ml)	16.9 (10.0, 82.0)[b]	23.5 (10.0, 162.7)[b]	0.1530
Surgical factors			
Surgical procedures, major (%)[c]	34.8	50.4	0.0045
Operation time (min)	285 (240, 350)[b]	278 (235, 353)[b]	0.5606
Blood loss (g)	780 (474, 1303)[b]	1000 (600, 1838)[b]	0.0015
Surgical margin (mm)	3.0 (0.0, 9.0)[b]	5.0 (1.0, 10.0)[b]	0.0411
Pathological data			
Macroscopic classification (SN/SNEG/CMN)	95/9/31	159/55/16	<0.0001
Tumor size (cm)	2.2 (1.6, 3.2)[b]	3.7 (2.8, 6.0)[b]	<0.0001
Histological differentiation (well/moderate/poor)	38/71/26	1/152/77	<0.0001
Septal formation (%)	59.3	73.4	0.0073
Serosal infiltration (%)	37.0	49.1	0.0292
Portal venous invasion (%)	25.9	48.3	<0.0001
Hepatic venous invasion (%)	14.8	18.3	0.4709
Bile ductal invasion (%)	3.7	7.4	0.1775
Intrahepatic metastasis (%)	23.0	30.9	0.1169
Edmondson classification (I or II/III or IV)	94/41	114/116	0.0002
Noncancerous liver (noncirrhosis/cirrhosis)	75/60	124/106	0.8277

[a] Median (standard deviation)

[b] Median (25th and 75th percentile)

[c] Segmentectomy, lobectomy or extended lobectomy

NC noncapsular type, *FC* fibrous capsular type, *HBs-Ag* hepatitis B virus antigen, *HCV-Ab* hepatitis C virus antibody, *ALP* alkaline phosphatase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, ICG_{15} indocyanine green retention rate at 15 min, *AFP* α-fetoprotein, *SN* single nodular, *SNEG* single nodular with extranodular growth type, *CMN* confluent multinodular

5 years was 95.9%, 87.7%, and 74.9%, and that for EC type at 1, 3, and 5 years was 92.6%, 77.2%, and 59.5%, respectively (Fig. 5b). Analysis of overall survival revealed that patients with EC type tended to have poorer outcomes than those with IC type ($P = 0.0973$). Furthermore, a multivariate proportional hazard model revealed that EC type ($P = 0.0482$), aspartate aminotransferase (AST) ≥53 IU/l ($P = 0.0002$), intrahepatic metastasis ($P = 0.0008$), and a cirrhotic liver ($P = 0.0107$) were independent prognostic factors for disease-free survival, while EC type was not an independent factor for overall survival ($P = 0.5995$; Table 3).

DISCUSSION

Early hepatocellular carcinoma (HCC) is generally an ill-demarcated nodule and has no complete fibrous capsule, defined as noncapsular (NC) type. Occurrence of the

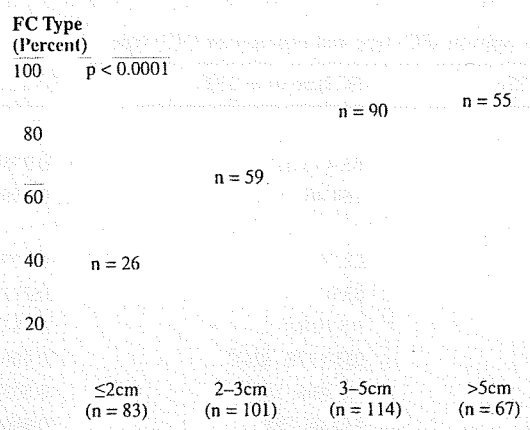

FIG. 2 Percentage of fibrous capsular (FC) type shown with reference to each tumor diameter: ≤2, 2–3, 3–5, and >5 cm. More FC type was observed as the tumor grew ($P < 0.0001$)

fibrous capsule in HCC is closely related to tumor size, and the tumor comes to be defined as intracapsular (IC) type of fibrous capsular (FC) type.[9] The fibrous capsule is recognized as a barricade preventing spread of cancer cells, but cancer cells infiltrate the fibrous capsule and the surrounding liver parenchyma as the tumor grows, changing from IC type to extracapsular infiltrating (EC) type.[2,12] Macroscopically, HCC progresses from single nodular type to single nodular with extranodular growth type or confluent multinodular. As the degree of infiltration to the fibrous capsule (fc-inf) becomes severe, the resulting the fibrous capsule becomes indistinct. This hypothetical series of progression in HCC is shown schematically in Fig. 6.

The tumor diameter, including Okuda staging accounts for one of the factors correlated with progression of HCC.[13–16] How the fibrous capsule is formed is not known, but the formation of the fibrous capsule results from the interaction between the tumor and host liver and interferes with the growth and invasion of the HCC.[17] In this study, the fibrous capsule came to be observed as the tumor diameter increased. This result might support the previous report by Ishizaki et al.[12] Furthermore, as the tumor grew, the frequency of EC type significantly increased in HCC. In Fig. 6, IC type, represented single nodular type progresses and the cancer cells penetrate the fibrous capsule and then EC type is exhibits those morphological features. Therefore, fc-inf is thought to demonstrate the morphologically invasive feature of HCC.

The clinicopathological relevance of the presence of the fibrous capsule in HCC has been reported.[17–21] It has been reported that encapsulated HCCs showed much lower incidence of direct invasion, tumor microsatellites, and vascular invasion, and more favorable outcome than non-encapsulated HCCs.[17–21] In our results, NC type had lower incidences of portal venous invasion and showed good differentiation and more favorable outcome than FC type. In Fig. 6, NC type includes small nodular type with indistinct margin, indicating early HCC, and single nodular with extranodular growth type or confluent multinodular, thus indicating advanced HCC. Because of the recent progress in early diagnosis, early HCCs are diagnosed and resected, and the fraction of resected HCCs less than 2 cm in diameter is 17.6% in Japan.[22–24] In the current study, median tumor size in NC type was 2.2 cm. The current results were thought to show a discrepancy with the previous results.[17–21]

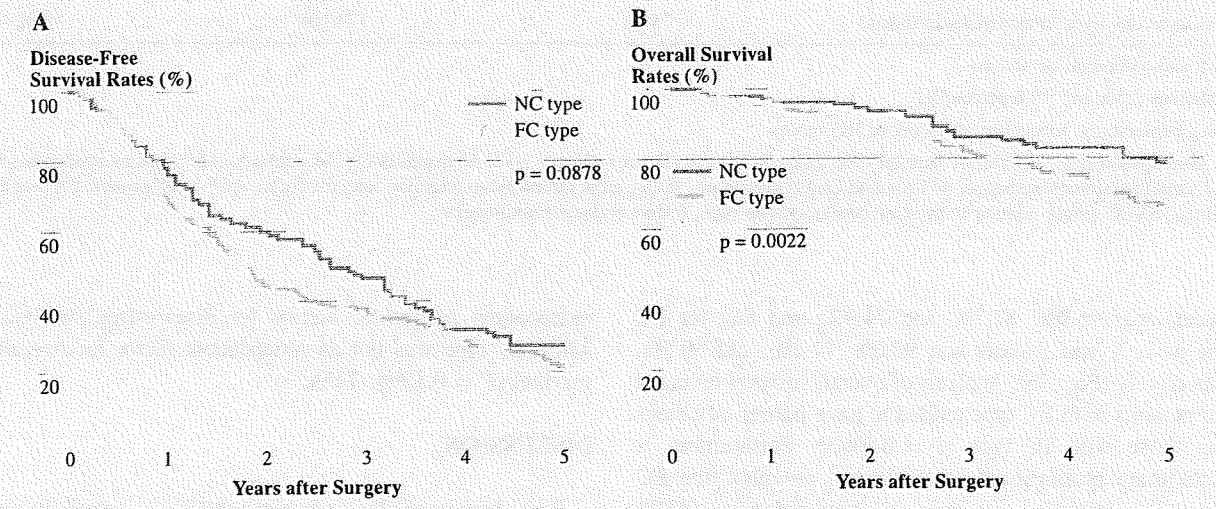

FIG. 3 Disease-free survival (**a**) and overall survival (**b**) curves for the fibrous capsule (FC) type versus the noncapsular (NC) type in 365 patients with HCC ($P = 0.0878$ and $P = 0.0022$, log-rank test). *Solid line* FC type, *dotted line* NC type

TABLE 2 Comparative analysis of the clinicopathological findings between extracapsular infiltrating (EC) type and intracapsular (IC) type

	IC type (n = 105)	EC type (n = 125)	P value
Clinical factors			
Age (years)	63.0 (7.3)[a]	63.7 (9.4)[a]	0.5254
Sex (male/female)	86/19	98/27	0.6199
Viral infection			
HBs-Ag (+) (%)	19.0	25.8	0.2685
HCV-Ab (+) (%)	64.8	61.6	0.6814
Albumin (g/dl)	3.8 (0.4)[a]	3.8 (0.4)[a]	0.8731
ALP (U/l)	248 (191, 310)[b]	251 (179, 326)[b]	0.8252
Total bilirubin (mg/dl)	0.8 (0.6, 1.1)[b]	0.8 (0.6, 1.0)[b]	0.4530
AST (IU/l)	52 (41, 74)[b]	53 (36, 79)[b]	0.6189
ALT (IU/l)	58 (38, 84)[b]	59 (34, 91)[b]	0.9929
Platelet ($\times 10^4/\mu l$)	11.6 (9.4, 16.2)[b]	13.1 (9.6, 16.4)[b]	0.5885
Prothrombin time (s)	87 (77, 100)[b]	90 (80, 100)[b]	0.2762
ICG_{15} (%)	17.8 (12.2, 25.0)[b]	14.4 (9.8, 20.4)[b]	0.0077
AFP (ng/mL)	24.6 (10.0, 104.7)[b]	23.5 (10.0, 162.7)[b]	0.8317
Surgical factors			
Surgical procedures, major (%)[c]	42.9	56.8	0.0468
Operation time (min)	310 (250, 364)[b]	278 (235, 353)[b]	0.2468
Blood loss (ml)	1000 (600, 1850)[b]	1000 (600, 1838)[b]	0.9651
Surgical margin (mm)	5.0 (1.0, 14.0)[b]	5.0 (1.0, 10.0)[b]	0.3259
Pathological data			
Macroscopic classification (SN/SNEG/CMN)	87/15/3	72/40/13	0.0001
Tumor size (cm)	3.3 (2.4, 4.3)[b]	3.7 (2.8, 6.0)[b]	0.0052
Histological differentiation (well/moderate/poor)	1/72/32	0/80/45	0.3885
Septal formation (%)	71.4	75.0	0.5524
Serosal infiltration (%)	43.8	53.6	0.1475
Portal venous invasion (%)	41.9	53.6	0.0860
Hepatic venous invasion (%)	14.3	21.6	0.1729
Bile ductal invasion (%)	4.8	9.6	0.2087
Intrahepatic metastasis (%)	21.9	38.4	0.0097
Edmondson classification (I or II/III or IV)	60/45	54/71	0.0468
Noncancerous liver (noncirrhosis/cirrhosis)	50/55	74/51	0.0858

[a] Median (standard deviation)

[b] Median (25th and 75th percentile)

[c] Segmentectomy, lobectomy or extended lobectomy

IC intracapsular type, *EC* extracapsular infiltrating type, *HBs-Ag* hepatitis B virus antigen, *HCV-Ab* hepatitis C virus antibody, *ALP* alkaline phosphatase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *PT* prothrombin time, ICG_{15} indocyanine green retention rate at 15 min, *AFP* α-fetoprotein, *SN* single nodular, *SNEG* single nodular with extranodular growth type, *CMN* confluent multinodular

HCC progresses from capsular invasion to intrahepatic metastasis through venous invasion.[25] In the current study, there were no significant differences with respect to portal venous invasion between EC and IC type; however, EC type showed significantly higher intrahepatic metastasis than IC type, and EC type was one of the independent prognostic factors for disease-free survival. Not surprisingly, EC type was also an independent prognostic factor for disease-free survival of 365 patients, including NC type (data not shown). These results might support the previous report and they verify that the new definition of fc-inf proposed has biological significance and predictive power for survival in HCC as well as in other neoplasm.[2,9,12,25–31]

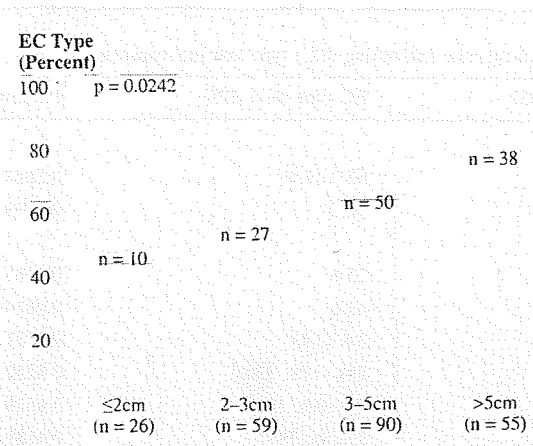

FIG. 4 Percentage of extracapsular infiltrating (EC) type in tumors with diameter ≤2, 2–3, 3–5, and >5 cm were 58.6% ($n = 17$), 45.8% ($n = 27$), 55.6% ($n = 50$), and 69.1% ($n = 38$), respectively. More EC type was observed as the tumor grew ($P = 0.0242$). *Shaded area* percentage of EC type

TABLE 3 Multivariate analysis for hepatocellular carcinoma, extracapsular infiltrating (EC) type versus intracapsular (IC) type

Variables	Hazard ratio	95% CI	*P* value
Disease-free survival			
AST >53 IU/l	1.889	1.348–2.646	0.0002
Intrahepatic metastases (+)	1.793	1.275–2.522	0.0008
Liver cirrhosis	1.545	1.107–2.156	0.0107
EC type	1.405	1.003–1.968	0.0482
Overall survival			
Intrahepatic metastases (+)	3.161	2.136–4.679	<0.0001
AST >53 IU/l	1.719	1.148–2.575	0.0085
EC type	1.557	0.994–2.440	0.5995

CI confidence interval, *AST* aspartate aminotransferase, *EC* extracapsular infiltrating type

Most macroscopic classification of HCC can be predicted by preoperative diagnostic imaging, such as computed tomography and angio-computed tomography.[11] The frequency of vascular invasion or intrahepatic metastases was higher in HCC of single nodular with extranodular growth type than that of single nodular type.[11,22] In the current result, single nodular with extranodular growth type and confluent multinodular were significantly affected by EC type in comparison with single nodular type, based on logistic regression analysis. Therefore, if presence of fc-inf is predicted by preoperative diagnostic imaging, which implies the macroscopic classification, the prediction might lead to new treatment strategies, including preoperative arterial chemoembolization and surgical procedures such as increasing surgical margin.

The current study verified the relevance of the new definition of fc-inf proposed, using a large series.[9] Fc-inf, a phenotype in which the cancer cells penetrate into the fibrous capsule and achieve direct contact with the surrounding liver parenchyma, is considered to be a novel marker for predicting prognosis, and presence of fc-inf might be predicted by gross features of the tumor.

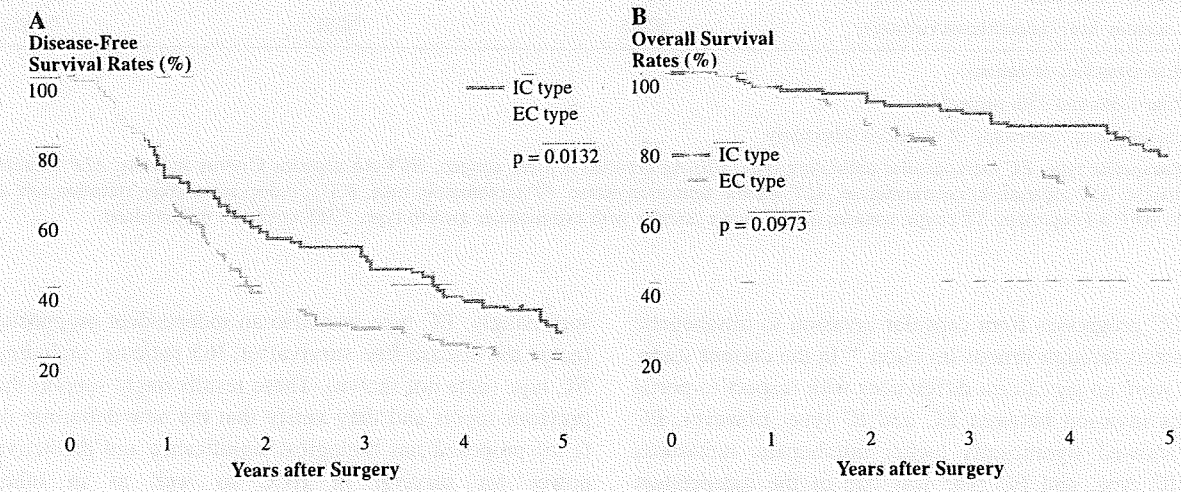

FIG. 5 Disease-free survival (**a**) and overall survival (**b**) curves for extracapsular infiltrating (EC) type versus intracapsular infiltrating (IC) type in 233 patients with HCC ($P = 0.0132$ and $P = 0.0973$, log-rank test). *Solid line* EC type, *dotted line* IC type. Solid line histologically defined fibrous capsule, dotted line histologically undetected fibrous capsule

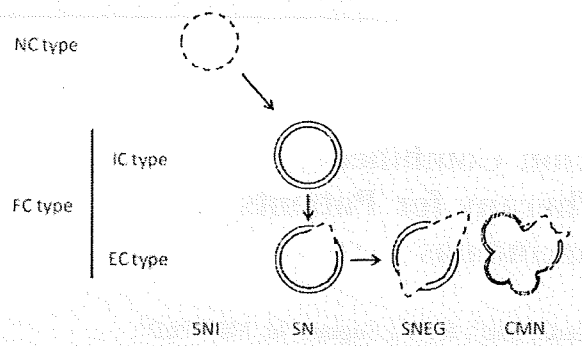

FIG. 6 Schematic drawing of macroscopic progression in HCC. The tumor is gradually covered by the fibrous capsule, according to tumor growth and degree of differentiation, with progression from NC type to FC (or IC) type. Cancer cells infiltrate through the fibrous capsule (EC type). Macroscopically, the tumor changes from single nodular type to single nodular with extranodular growth type or confluent multinodular. *SNI* single nodular type with indistinct margin, *SN* single nodular, *SNEG* single nodular with extranodular growth type, *CMN* confluent multinodular, *NC type* noncapsular type, *FC type* fibrous capsular type, *EC type* extracapsular infiltrating type, *IC type* intracapsular type

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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Long-Term Results of Hepatic Resection Combined with Intraoperative Local Ablation Therapy for Patients with Multinodular Hepatocellular Carcinomas

Shinji Itoh, MD, PhD[1,2], Kazutoyo Morita, MD[1], Shigeru Ueda, MD[1], Keishi Sugimachi, MD, PhD[1], Yo-ichi Yamashita, MD, PhD[1], Tomonobu Gion, MD, PhD[1], Kengo Fukuzawa, MD, PhD[2], Kenzo Wakasugi, MD, PhD[2], Akinobu Taketomi, MD, PhD[1], and Yoshihiko Maehara, MD, PhD, FACS[1]

[1]Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [2]Department of Surgery, Oita Red Cross Hospital, Oita, Japan

ABSTRACT

Background. Recently, local ablation therapy has been widely used for treatment of small hepatocellular carcinoma (HCC). The present study assessed the outcome of hepatic resection combined with intraoperative local ablation therapy in patients with multinodular HCCs.

Methods. Forty-one patients with initial and multinodular HCCs underwent hepatic resection combined with intraoperative local ablation therapy. The mean maximum diameter of all tumors was 3.8 cm (range 2.1–16.0 cm), and the mean number of nodules was 3.2 (range 2–11). We evaluated the survival rates and assessed the prognostic factors associated with overall survival rates using Cox proportional hazard models.

Results. Intraoperative local ablation therapy was completed in all patients with no evidence of residual viable tumor on the first postoperative computed tomography (CT) scan. The 3-, 5- and 7-year overall survival rates were 84.3%, 61.2%, and 61.2%, respectively. Patients with preoperative des-gamma carboxyprothrombin (DCP) level >300 mAU/ml showed significantly worse overall survival than those with DCP level ≤300 mAU/ml ($P < 0.01$).

Conclusions. Hepatic resection combined with intraoperative local ablation therapy is effective for multinodular HCCs. DCP >300 mAU/ml was a significant prognostic factor of long-term overall survival.

Recently, notable advances have been made in the surgical management of patients with hepatocellular carcinoma (HCC). Several studies have reported improved outcomes of patients with HCC who have undergone liver resections, including not only decreases in operative mortality and morbidity, but also favorable long-term results.[1–4] Hepatic resection remains the best hope for a cure but is suitable in only 9–27% of patients.[5,6] The presence of significant background cirrhosis or of multinodular tumors often precludes liver resection in patients with HCCs. Liver transplantation has also offered prolonged disease-free and overall survival for carefully selected patients with small HCCs but has been limited in countries such as Japan where cadaveric organ harvesting is very limited.[7,8] In recent years, local ablation therapies [ethanol injection therapy (EIT), microwave coagulation therapy (MCT), and radiofrequency ablation (RFA)] have emerged as safe and effective treatments of small HCC.[9] However, percutaneous local ablation therapy had poor local control in patients with nodules more than 2 cm in diameter and multiple nodules.[10] We have therefore advocated a new strategy of hepatic resection combined with intraoperative local ablation therapy for patients with multinodular HCCs. Here we present the results of performing hepatic resection combined with intraoperative local ablation therapy for multinodular HCCs in patients. We evaluate the validity and identify the prognostic factors of hepatic resection combined with intraoperative local ablation therapy for patients with multinodular HCCs.

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S. Itoh, MD, PhD
e-mail: itoshin@surg2.med.kyushu-u.ac.jp

METHODS

Patient Characteristics

From January 1997 to December 2004, 342 patients with nodular HCCs underwent hepatic resection at the Department of Surgery and Science, Kyushu University Hospital. Of these, 78 patients with multinodular HCCs underwent hepatic resection combined with intraoperative local ablation therapy. Patients who underwent hepatic resection for main HCCs larger than 2 cm in diameter and intraoperative local ablation therapy for remnant nodules smaller than or equal to 2 cm in diameter were selected. Twenty-eight patients had this operation carried out for recurrent HCC; therefore, 41 patients with initial and multinodular HCCs were the subjects of this study, and were compared with 179 patients with main HCCs larger than 2 cm in diameter who underwent only primary hepatic resection during the same period.

All patients underwent thorough examination including laboratory tests to evaluate liver function, tumor marker such as alpha-fetoprotein (AFP), and des-gamma carboxyprothrombin (DCP), radiological assessment of tumor location and resectability by ultrasonography, computed tomography (CT), magnetic resonance imaging, mesenteric arteriography, and computed tomographic portography. We did not perform percutaneous tumor biopsy to diagnose HCC because it might cause peritoneal dissemination. When it was difficult to determine preoperatively whether small hepatic nodules were HCC or not, we performed intraoperative tumor biopsy. Patients included 32 men and 9 women, with mean age of 63.3 ± 9.7 (standard deviation, SD) years and a range of 31–75 years.

Surgical Procedures

On the basis of multiple tumor locations or presence of cirrhosis with functional hepatic reserve, all 41 patients were judged not to be able to tolerate the necessary hepatic resection. Indications for hepatic resection and type of operative procedure for main HCC were determined according to preoperative indocyanine green retention rate at 15 min (ICGR15). ICGR15 <30% indicated anatomic resection, and ICGR15 ≥30% indicated limited resection.[2] Two-thirds of nontumorous liver parenchyma could be removed if ICGR15 was ≤10%, and less than one-third of it could be resected if ICGR15 was 10–19%; patients with ICGR15 of 20–29% received single segmentectomy or less based on Couinaud's classification.[11] All patients met the following criterion for hepatic resection combined with intraoperative local ablation therapy: one or more small (≤2 cm maximum diameter) HCCs adequate for intraoperative local ablation therapy expected to remain after hepatic resection. The hepatic resection procedures consisted of a right trisegmentectomy in 1 patient, extended right lobectomy in 2 patients, segmentectomy in 8 patients, subsegmentectomy in 7 patients, and limited resection in 23 patients. Local ablation therapies such as MCT, RFA, and EIT were indicated for small HCCs under intraoperative ultrasonography guidance. MCT and RFA were generated by a magnetron in a microwave generator (Microtaze OT-110 M, HS-15 M; Azwell Co., Osaka, Japan) and an RF generator (Cool-tip RF System, CMI Century Medical Co., Inc., Tokyo, Japan). EIT was performed for small HCC near the Glisson branch using 21-gauge needles measuring 15 cm in length. Local ablation therapies are shown in Table 1.

TABLE 1 Local ablation therapies for small hepatocellular carcinomas

Variables	Number of nodules
MCT	60
RFA	9
EIT	1

MCT microwave coagulation therapy, *RFA* radiofrequency ablation, *EIT* ethanol injection therapy

Follow-Up

After discharge, all patients were examined for recurrence by ultrasonography and tumor markers every month and by dynamic computed tomography every 3 months.[3] Median follow-up period after operation was 3.1 years (range 0.1–8.6 years). When recurrence of HCC was suspected, additional examinations such as angiography and magnetic resonance imaging were performed. We treated recurrent HCC by repeat hepatic resection, local ablation therapy, and lipiodolization.[12,13]

Statistical Analysis

Categorical variables were compared using Fisher's exact test. Continuous variables with a normal distribution are presented as mean (SD) and compared using Student's *t* test; the others are presented as median (range) and compared using the Mann–Whitney *U* test. Overall survival curves and disease-free survival curves were drawn according to the Kaplan–Meier method and compared using the log-rank test.[14] Patient survival and disease-free survival after hepatic resection combined with intraoperative local ablation therapy were compared using the following clinicopathologic variables. Background factors were age, sex, hepatitis B viral infection, hepatitis C viral infection, albumin, total bilirubin, prothrombin time, ICGR15, alanine transaminase, platelet count, Child–Pugh

classification, and the histologic findings of the noncancerous part. Operative factors were operative procedure (hepatic resection, and the local ablation therapy) and surgical margin. Tumor-related factors were maximum tumor diameter, tumor number, tumor location, Milan criteria, histologic findings (histology classified by Edmondson and Steiner, tumor cell differentiation, capsular formation, invasion to portal vein), preoperative AFP, and preoperative DCP.[15,16] The Cox proportional hazards model with stepwise procedure was used in multivariate analysis of survival data.[17] All statistical differences were deemed significant at the level of $P < 0.05$.

RESULTS

The maximal diameter of all resected tumors ranged from 2.1 to 16.0 cm (mean ± SD, 3.8 ± 3.2 cm). The number of resected nodules was 1.5 ± 1.2 (SD) with a range of 1–7. The number of nodules on which local ablation therapy was performed was 1.7 ± 1.3 (SD) with a range of 1–6. The median diameter of surgical margin in the hepatic resection combined with intraoperative local ablation therapy was 4 mm (range 0–40 mm), and those of surgical margin in the limited and anatomical hepatic resections were 3.5 mm (range 0–20 mm) and 5 mm (range 0–40 mm). There was no significant difference in surgical margin between limited and anatomical hepatic resections combined with intraoperative local ablation therapy. Intraoperative local ablation therapy was complete in all patients with no evidence of residual viable tumor on the first postoperative CT scan.

Table 2 shows a comparison of the clinicopathological factors between patients who underwent hepatic resection combined with intraoperative local ablation therapy and only primary hepatic resection. Patients who underwent hepatic resection combined with intraoperative local ablation therapy had significantly lower levels of prothrombin time, ICGR15 score, platelet count, main tumor size, and DCP, and a large number of limited resection, histological liver cirrhosis, and nodules compared with patients who underwent only primary hepatic resection. The rates of surgical margin positivity, which was defined as the exposure of cancer cells in the pathological finding, between patients who underwent hepatic resection combined with intraoperative local ablation therapy and only primary hepatic resection were 0% and 2.8%. In this study, surgical margin positivity was not a primary risk factor for local recurrence.

Overall and disease-free survival curve are illustrated in Fig. 1a and b. The 3-, 5- and 7-year overall survival rates in

TABLE 2 Clinicopathological data for patients with hepatocellular carcinomas

Variables	Hx + Abl ($n = 41$)	Hx ($n = 179$)	P[c]
Background factors			
Age (years)[a]	63.3 ± 9.7	63.7 ± 9.7	NS[d]
Sex (male/female)	32/9	146/33	NS
Positive HBs-Ag	10 (24.4%)	35 (19.6%)	NS
Positive HCV-Ab	27 (65.9%)	107 (59.8%)	NS
Albumin (g/dl)[b]	3.9 (2.8–4.4)	3.9 (2.8–4.8)	NS[e]
Total bilirubin (mg/dl)[b]	0.8 (0.3–3.0)	0.8 (0.4–2.6)	NS[e]
Prothrombin time (%)[b]	79 (52–120)	85 (62–140)	<0.05[e]
ICGR15 (%)[b]	21.6 (1.6–55.6)	14.9 (1.4–43.1)	<0.01[e]
ALT (IU/l)[b]	61 (13–145)	46 (9–300)	NS[e]
Platelets ($\times 10^4/mm^3$)[b]	10.8 (5.3–32.8)	14.1 (2.7–46.6)	<0.01[e]
Child–Pugh classification (A/B)	34/7	158/21	NS
Histological liver cirrhosis	22 (53.7%)	54 (30.2%)	<0.01
Operative factors			
Anatomical resection	18 (43.9%)	130 (72.6%)	<0.01
Limited resection	23 (56.1%)	49 (27.4%)	
Surgical margin (mm)[b]	4 (0–40)	3 (0–55)	NS[e]
Surgical margin positivity (%)	0 (0%)	5 (2.8%)	NS
Tumor-related factors			
Main tumor size (cm)[b]	2.9 (2.1–16.0)	3.8 (2.1–17.5)	<0.01[e]
Numbers of nodules[b]	2 (2–11)	1 (1–4)	<0.01[e]
Microscopic portal venous invasion	12 (29.3%)	93 (52.0%)	<0.05
AFP (ng/ml)[b]	22.3 (2.1–32,879)	23.6 (1–410,600)	NS[e]
DCP (mAU/ml)[b]	36.5 (12–63,849)	191 (12–75,000)	<0.01[e]

NS not significant, *Hx + abl* hepatic resection combination with intraoperative local ablation therapy, *Hx* only primary hepatic resection, *HBs-Ag* hepatitis B surface antigen, *HCV-Ab* hepatitis C virus antibody, *ICGR15* indocyanine green retention rate at 15 min, *ALT* alanine transaminase, *AFP* alfa-fetoprotein, *DCP* des-gamma carboxyprothrombin

[a] Mean (SD)

[b] Median (range)

[c] Fisher's exact test unless indicated otherwise

[d] Student's *t* test

[e] Mann–Whitney *U* test

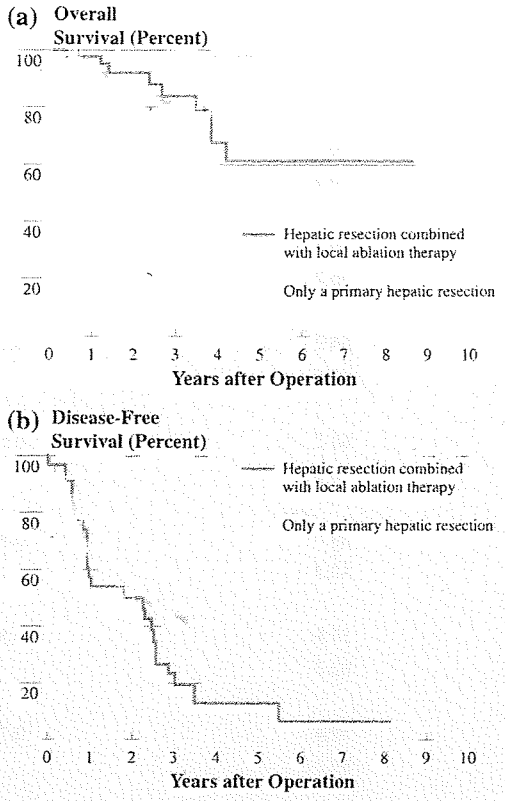

FIG. 1 Overall (a) and disease-free (b) survival curve after hepatic resection combined with local ablation therapy for 41 patients with multinodular HCCs (*solid line*) and after only a primary hepatic resection for 179 patients with main HCC larger than 2 cm in diameter (*dashed line*)

patients with hepatic resection combined with intraoperative local ablation therapy were 84.3%, 61.2%, and 61.2%, respectively. The 3-, 5-, and 7-year overall survival rates in patients with only a primary hepatic resection were 80.7%, 75.5%, and 71.0%, respectively. Survival after hepatic resection combined with intraoperative local ablation therapy did not substantially differ from that of patients who underwent only primary hepatic resection. The 3-, 5-, and 7-year disease-free survival rates in patients with hepatic resection combined with intraoperative local ablation therapy were 23.1%, 12.8%, and 6.4%, respectively. The 3-, 5-, and 7-year disease-free survival rates in patients with only primary hepatic resection were 46.1%, 30.8%, and 22.3%, respectively. Disease-free survival after hepatic resection combined with intraoperative local ablation therapy tended to be poor compared with that of patients who underwent only primary hepatic resection ($P = 0.09$).

Table 3 presents preoperative, operative, and tumor-related demographics of the patients with multinodular HCCs. There were no significant differences in overall survival based on the background factors. Postoperative results exhibited no significant differences between anatomical resection and limited resection, or between MCT and RFA. Patients with preoperative DCP level >300 mAU/ml showed significantly worse overall survival than those with DCP level ≤300 mAU/ml. The Cox proportional hazards regression model was used to assess the effect of different variables on overall survival. Multivariate analysis identified one poor prognostic factor, DCP > 300 mAU/ml, as influencing overall survival rate (Table 4).

We classified the multinodular HCCs on the basis of findings including preoperative ultrasonography, dynamic computed tomography, magnetic resonance imaging, angiography, intraoperative ultrasonography, and intraoperative tumor biopsy. Twenty-nine of 41 patients were classified as multicentric (MC) occurrence of HCCs, and 12 patients of 41 were classified as intrahepatic metastasis (IM) of HCCs. Clinicopathological data were compared between patients with MC and IM of HCCs. Table 5 shows a comparison of clinicopathological factors between patients with MC and IM of HCCs. Patients with IM of HCCs had significantly higher levels of main tumor size and DCP, and higher rates of microscopic portal venous invasion and exceeding the Milan criteria compared with patients with MC of HCCs. Overall survival curve are illustrated in Fig. 2. The 5-year overall survival rates in patients with MC and IM of HCCs were 77.8% and 33.0%, respectively. Patients with IM of HCCs showed significantly worse overall survival than those with MC of HCCs ($P = 0.0230$, log-rank test).

DISCUSSION

The aim of our study was to evaluate the validity of hepatic resection combined with local ablation therapy for patients with multinodular HCCs. Hepatic resection combined with local ablation therapy was completed in all patients with no evidence of residual viable tumor. Survival after hepatic resection combined with intraoperative local ablation therapy did not differ substantially from that of the patients who underwent only primary hepatic resection, even if these patients differed in terms of background factors of liver function and tumor-related factors.

Favorable long-term results of hepatic resection have been reported.[3,4] On the other hand, good results have been reported with percutaneous application of local ablation therapy with small HCC, and laparoscopic local ablation therapy of HCC was reported.[18–21] However, only a few series of intraoperative local ablation therapy of HCC have been reported. Raut et al. performed open RFA without hepatic resection ($n = 32$) and open RFA with hepatic resection ($n = 22$) for patients with unresectable HCCs.[22] The 3- and 5-year overall survival rates in patients with

TABLE 3 Patient characteristics and overall survival

Variables		3-Year survival (%)	5-Year survival (%)	*P* value[a]
Background factors				
Age (years)				
0: <64	($n = 16$)	77.5	66.5	0.9455
1: ≥64	($n = 25$)	89.0	50.9	
Sex (male/female)				
1: male	($n = 32$)	81.4	60.1	0.5721
2: female	($n = 9$)	100	66.7	
HBs-Ag				
0: negative	($n = 31$)	91.3	54.2	0.7433
1: positive	($n = 10$)	62.5	62.5	
HCV-Ab				
0: negative	($n = 14$)	74.6	62.2	0.5123
1: positive	($n = 27$)	88.9	56.6	
Albumin (g/dl)				
0: >3.8	($n = 21$)	81.3	69.7	0.8347
1: ≤3.8	($n = 20$)	87.2	52.3	
Total bilirubin (mg/dl)				
0: <0.9	($n = 21$)	72.0	57.6	0.5823
1: ≥0.9	($n = 20$)	94.1	62.7	
Prothrombin time (%)				
0: ≥80	($n = 20$)	74.3	59.4	0.7564
1: <80	($n = 21$)	94.7	59.2	
ICGR15 (%)				
0: <22	($n = 21$)	73.6	58.9	0.7244
1: ≥22	($n = 20$)	94.1	58.8	
ALT (IU/l)				
0: <67	($n = 22$)	77.5	68.9	0.9246
1: ≥67	($n = 19$)	91.7	41.9	
Platelets ($\times 10^4/mm^3$)				
0: ≥11	($n = 19$)	83.0	56.9	0.6431
1: <11	($n = 21$)	85.7	62.5	
Child–Pugh classification				
1: A	($n = 34$)	80.2	57.1	0.3523
2: B	($n = 7$)	100	75.0	
Histological liver cirrhosis				
0: absent	($n = 19$)	85.9	47.7	0.5059
1: present	($n = 22$)	82.8	72.5	
Operative factors				
Hepatic resection				
1: anatomical	($n = 18$)	85.0	47.2	0.8283
2: limited	($n = 23$)	83.5	65.8	
Surgical margin (mm)				
0: ≥5	($n = 19$)	85.0	48.6	0.6646
1: <5	($n = 21$)	82.3	72.0	
MCT				
0: absent	($n = 5$)	50.0	50.0	0.8191
1: present	($n = 36$)	81.6	58.3	

TABLE 3 continued

Variables		3-Year survival (%)	5-Year survival (%)	*P* value[a]
RFA				
0: absent	(*n* = 35)	81.2	62.6	0.6312
1: present	(*n* = 6)	50.0	50.0	
Tumor-related factors				
Tumor size (cm)				
0: ≤3.0	(*n* = 20)	87.2	65.4	0.4037
1: >3.0	(*n* = 20)	80.2	55.0	
Tumor number				
0: <4	(*n* = 27)	92.9	63.7	0.1486
1: ≥4	(*n* = 14)	70.7	53.9	
Tumor location				
0: single lobe	(*n* = 16)	90.0	67.5	0.3111
1: bilateral lobe	(*n* = 25)	81.0	57.3	
Milan criteria				
0: met	(*n* = 18)	100	66.7	0.1961
1: not met	(*n* = 23)	74.0	58.3	
Histology				
0: grades 1 and 2	(*n* = 26)	88.3	49.7	0.9532
1: grade 3	(*n* = 14)	77.1	64.3	
Tumor differentiation				
0: well or moderately	(*n* = 30)	84.3	53.1	0.9739
1: poorly	(*n* = 10)	80.0	64.0	
fc				
0: absent	(*n* = 17)	83.3	83.3	0.1878
1: present	(*n* = 23)	86.0	45.9	
vp				
0: absent	(*n* = 28)	89.6	65.3	0.1828
1: present	(*n* = 12)	72.9	48.6	
AFP (ng/ml)				
0: ≤100	(*n* = 31)	87.3	62.2	0.6041
1: >100	(*n* = 9)	76.2	57.1	
DCP (mAU/ml)				
0: ≤300	(*n* = 33)	82.6	68.6	0.0064
1: >300	(*n* = 7)	68.6	0	

HBs-Ag hepatitis B surface antigen, *HCV-Ab* hepatitis C virus antibody, *ICGR15* indocyanine green retention rate at 15 min, *ALT* alanine transaminase, *MCT* microwave coagulation therapy, *RFA* radiofrequency ablation, *fc* capsular formation, *vp* invasion to the portal vein, *AFP* alfa-fetoprotein, *DCP* des-gamma carboxyprothrombin

[a] Statistics using the log-rank test

open RFA without hepatic resection were 55.1% and 45.9%, respectively. The 3- and 5-year overall survival rates in patients with open RFA with hepatic resection were 44.8% and 44.8%, respectively. In the study of Choi et al., 53 patients who had multifocal HCCs underwent hepatectomy combined with intraoperative RFA.[23] The cumulative survival rates at 3 and 5 years were 80% and 55%, respectively. In contrast, patients with unresectable HCCs who are treated with medical or best supportive care have median survival of 9–12 months, with 1- and 3-year survival rates of 44–55% and 13–26%, respectively.[24–27] In our report, we showed the results of hepatic resection combined with intraoperative local ablation therapy for 41 patients with multinodular HCCs, and that the 3- and 5-year overall survival rates were 84.3% and 61.2%, respectively. Base on these data, we believe that hepatic resection combined with local ablation therapy is a useful therapeutic option for patients with multinodular HCCs.

In this study, we selected patients who underwent hepatic resection for main HCC larger than 2 cm in

TABLE 4 Results of multivariate analysis using the Cox proportional hazards model

Variables	Hazard ratio	95% CI	*P* value
DCP >300 mAU/ml	6.48	1.40–30.0	0.0167

DCP des-gamma carboxyprothrombin, *CI* confidence interval

diameter, and performed intraoperative local ablation therapy for remnant nodules smaller than or equal to 2 cm in diameter after hepatic resection. According to the fourth edition of the *General Rules for the Clinical and Pathological Study of Primary Liver Cancer* published by the Liver Cancer Study Group of Japan, patients with HCCs that are multinodular and >2.0 cm in diameter are defined as stage III.[28] On the other hand, patients with HCCs that are multinodular and ≤2 cm in diameter are defined as stage II. Hepatic resection is recommended for patients with resectable HCCs. Recurrent rates after RFA are higher than those after resection.[29] Wakai et al. reported that favorable effects of hepatectomy on long-term survival compared with percutaneous ablation were seen in patients with tumors >2 cm.[30] In those patients with multinodular HCCs who cannot be treated with hepatic resection only, main HCCs should be resected first, and remnant nodules can then be treated with intraoperative local ablation therapy. Intraoperative local ablation therapy has advantages over the percutaneous procedure. Tumors near stomach, colon, kidney or diaphragm can be treated with intraoperative local ablation therapy. Intraoperative ultrasonography examination can identify very small hepatic nodules that may not be detected on preoperative imaging.[31,32] Taken together, we think it is adequate to use hepatic resection for main HCC larger than 2 cm in diameter, and intraoperative local ablation therapy for remnant nodules smaller than equal to 2 cm in diameter after hepatic resection.

Various kinds of indications have been reported as prognostic parameters for patients with HCC after hepatic resection or local ablation therapy, including clinical factors such as liver function of patients, tumor factors such as tumor size and tumor markers including AFP, surgical factors such as surgical margin, and pathological factors such as degree of histological differentiation and vascular invasion.[3,4,18,19,33] Choi et al. have reported that resected tumor size was a significant prognostic predictor of long-term survival for 53 patients who had multifocal HCCs and underwent hepatectomy combined with intraoperative RFA.[23] In our study, tumor size, tumor number, invasion of portal vein, and serum level of AFP were shown not to be significant overall survival in our univariate analysis. Patients with preoperative DCP level >300 mAU/ml had poor overall survival on multivariate analysis. Preoperative DCP level >300 mAU/ml was correlated with tumor size more than 3 cm in diameter ($P < 0.01$) and exceeding

TABLE 5 Clinicopathological data for patients with MC and IM of hepatocellular carcinomas

Variable	MC (n = 29)	IM (n = 12)	*P* value[b]
Background factors			
Age (years)[a]	66 (31–75)	66 (36–74)	NS[c]
Sex (male/female)	21/8	11/1	NS
Positive HBs-Ag	5 (17.2%)	5 (41.6%)	NS
Positive HCV-Ab	20 (69.0%)	7 (58.4%)	NS
Albumin (g/dl)[a]	3.8 (2.8–4.4)	3.95 (3.1–4.1)	NS[c]
Total bilirubin (mg/dl)[a]	1.0 (0.4–3.0)	0.65 (0.3–1.2)	<0.05[c]
Prothrombin time (%)[a]	76 (52–120)	91 (68–113)	NS[c]
ICGR15 (%)[a]	23.4 (1.6–55.6)	15.2 (3.8–48.0)	NS[c]
ALT (IU/l)[a]	69 (14–145)	39 (13–123)	NS[c]
Platelets ($\times 10^4/mm^3$)[a]	10.4 (5.3–17.3)	11.9 (6.3–32.8)	NS[c]
Child–Pugh classification (A/B)	23/6	11/1	NS
Histological liver cirrhosis	18 (62.1%)	4 (33.3%)	NS
Tumor related factors			
Main tumor size (cm)[a]	2.4 (2.1–16.0)	4.05 (2.5–15.0)	<0.01[c]
Number of nodules[a]	2 (2–11)	3 (2–8)	NS[c]
Milan criteria (met/not met)	16/13	2/10	<0.05
Microscopic portal venous invasion	4 (13.8%)	8 (66.7%)	<0.01
AFP (ng/ml)[a]	28.7 (5.9–4,746)	13.15 (2.1–32,879)	NS[c]
DCP (mAU/ml)[a]	25.5 (12–949)	270.5 (23–63,849)	<0.01[c]
No. with >300 mAU/ml	2 (6.9%)	5 (42.6%)	<0.05

NS not significant, *MC* multicentric occurrence, *IM* intrahepatic metastasis, *HBs-Ag* hepatitis B surface antigen, *HCV-Ab* hepatitis C virus antibody, *ICGR15* indocyanine green retention rate at 15 min, *ALT* alanine transaminase, *AFP* alfa-fetoprotein, *DCP* des-gamma carboxyprothrombin

[a] Median (range)

[b] Fisher's exact test unless indicated otherwise

[c] Mann–Whitney *U* test

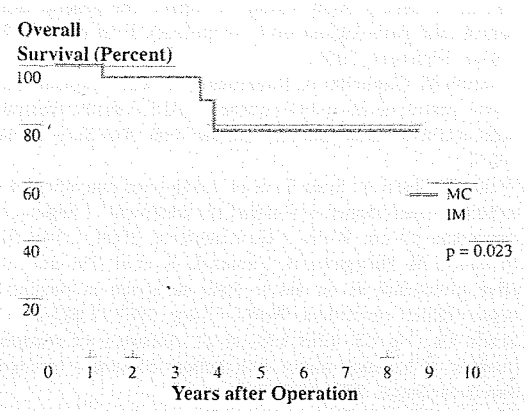

FIG. 2 Overall survival curve after hepatic resection combined with local ablation therapy for 29 patients with multicentric occurrence (MC) (*solid line*) and 12 patients with intrahepatic metastasis (IM) (*dashed line*) of HCCs. The overall survival curve between patients with MC and IM of HCCs showed a significant separation ($P = 0.023$, log-rank test)

Milan criteria ($P < 0.01$), with a tendency for portal venous invasion ($P = 0.09$) (data not shown). DCP has been well established as a sensitive and specific tumor marker in patients with HCC.[34,35] It has also been reported that DCP levels are associated with the development of portal venous invasion in patients with HCC after hepatic resection.[36,37] Furthermore, Koike et al. prospectively analyzed the development of portal venous invasion after percutaneous ethanol injection in 227 patients who did not have portal venous invasion when starting treatment.[38] They found that the serum level of DCP was the strongest predisposing factor for development of portal venous invasion, followed by the histologic grade of tumor differentiation. We also reported that preoperative DCP value >300 mAU/ml was strongly associated with high recurrence rate in patients who underwent living-donor liver transplantation for HCC.[39] These findings suggest that higher DCP with multinodular HCCs reveals the existence of portal venous invasion which could not be treated by local ablation therapy.

Were the present results useful in order to select the hepatic resection combined with intraoperative local ablation therapy or liver transplantation as a more adequate management for patients with multinodular HCCs? In this study, Patients with IM of HCCs had significantly higher levels of main tumor size and DCP, a large number of microscopic portal venous invasion and exceeding the Milan criteria, and worse overall survival compared with patients with MC of HCCs. We reported that tumor size >5 cm and DCP level >300 mAU/ml were independent factors for the recurrence of HCC after LDLT.[40] In the study of Ito et al., the 40 patients who presented with tumor size >5 cm, DCP level >400 mAU/ml, and tumor number >10 showed significantly worse overall survival after LDLT compared with the 78 patients who presented with tumor size ≤5 cm, DCP level ≤400 mAU/ml, and tumor number ≤10 (5-year survival: 86.7% versus 34.4%, respectively; $P < 0.01$).[41] Together with our study, we think that liver transplantation might be a more adequate management for patients with MC of HCCs and low level of DCP, and aggressive hepatic resection combined with intraoperative local ablation therapy might be indicated for patients with IM of HCCs and high level of DCP. This management strategy may improve chances of long-term survival in patients with advanced-stage multinodular HCCs including larger tumor size and higher level of DCP. Further investigation of a greater number of patients is needed to confirm our encouraging results.

In conclusion, hepatic resection combined with intraoperative local ablation therapy is effective for multinodular HCCs and may improve long-term survival in patients with advanced HCCs. Preoperative DCP value is shown to be a useful strong prognostic factor of long-term survival.

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Early Outcome Following Hepatic Resection in Patients Older Than 80 Years of Age

Ken Shirabe · Kiyoshi Kajiyama · Norifumi Harimoto · Tomonobu Gion · Eiji Tsujita · Tomoyuki Abe · Shigeki Wakiyama · Takashi Nagaie · Yoshihiko Maehara

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Abstract

Background We aimed to study the early outcome of patients 80 years of age and older undergoing liver resection and to compare the results with the outcomes of patients younger than 80 years of age.

Methods All 350 consecutive patients undergoing hepatic resections from 2004 April to 2008 October were included. Patients were divided into two groups: 80 years of age and older (group I; $n = 43$) and less than 80 years of age (group II; $n = 307$). Preoperative clinicopathological features, intraoperative factors, in-hospital mortality, postoperative complications, length of hospital stay, operative mortality, morbidity, and prognosis after discharge were analyzed and compared between groups I and II.

Results There was no significant difference between the two groups regarding the indication for hepatic resection. Hepatitis viral status was significantly different between groups: patients without hepatitis B or C viral infection were more common in group I than in group II. Regarding preoperative liver function, serum levels of albumin were significantly lower in group I than in group II. Although the operative time was significantly shorter in group I than in group II, no difference was found between groups regarding such operative factors as type of hepatectomy, blood loss, and rate of blood transfusion. After elimination of 16 patients with extrahepatic bile duct resection and reconstruction, no difference existed between the two groups in operative time. There was no postoperative mortality nor in-hospital mortality in group I; in group II one postoperative death (0.3%) and two in-hospital deaths (0.6%) were recorded. There was no difference between groups in the incidence of morbidity and early prognosis after discharge.

Conclusions The results indicate that hepatic resection for elderly patients over 80 can be safely performed given careful patient selection.

Introduction

The age of patients with malignancies of the liver has been increasing in Japan; this has led several groups to analyze the feasibility of hepatic resections in aged subjects [1–12]. To date, sufficient evidence exists that hepatectomy can be safely performed in selected elderly patients. Nevertheless, most previously published reports define aged patients as those older than the age of 65 or 70 years [1, 2, 4–12]. Our goal was to evaluate the efficacy of the procedure in those over the age of 80 years.

Regardless of the indications for surgery and the extent of planned liver resections, this population is more likely to suffer from associated diseases, such as cardiac or pulmonary dysfunction and diabetes mellitus, which may affect postoperative outcome.

K. Shirabe
Department of Hepatogastroenterological Surgery, Aso Iizuka Hospital, Iizuka City 820-8505, Japan

K. Kajiyama · N. Harimoto · T. Gion · E. Tsujita · T. Abe · S. Wakiyama · T. Nagaie
Department of Surgery, Aso Iizuka Hospital, Iizuka City 820-8505, Japan

K. Shirabe (✉) · Y. Maehara
Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
e-mail: kshirabe@surg2.med.kyushu-u.ac.jp; kshirabeh1@aih-net.com