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Prognosis after hepatic resection in patients with hepatocellular carcinoma, estimated on the basis of the morphometric indices

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Abstract. To determine whether the morphometric indices of hepatocellular carcinoma (HCC) correlated with the prognoses, the microscopic morphometric values for 84 HCC cases treated by hepatic resection were studied using an image analyzer in relation to the survival rate and the gross classification. The mean survival time (MST) was 58 months in cases with a nucleocytoplasmic area ratio (N/C) of less than 0.28; this was significantly longer than the 38-month MST in cases with an N/C of more than 0.28 (P <0.05). In stage III disease, the MST for cases with an N/C of less than 0.28 was 63 months, which was significantly longer than the MST of 13 months for cases with an N/C of more than 0.28. After relatively noncurative hepatic resection, the MST for cases with an N/C of less than 0.28 was 49 months, and this was significantly longer than the MST of 8 months for cases with an N/C of more than 0.28. The MST was 71 months for cases with a coefficient of variance of the nuclear form factor (NCV) of less than 5.5%, which was significantly longer than the MST of 33 months for cases with an NCV of more than 5.5% (P <0.05). In stage III disease, the MST was 69 months for cases with an NCV of less than 5.5%, and this was significantly longer than the MST of 29 months for cases with an NVC of more than 5.5% (P <0.05). In cases with an N/C of less than 0.28, 18% had vascular invasion and 38% had intrahepatic metastases, whereas in those with an N/C of more than 0.28, 62% had vascular invasion and 67% had intrahepatic metastases (P <0.01, P <0.05). Based on the results of these morphometric studies on HCC cases treated by hepatic resection, N/C and NCV may be useful as prognostic factors.

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Introduction

Recent advances in the imaging of hepatocellular carcinoma (HCC) have increased the number of resectable cases and have shown marked improvement in the postoperative prognosis [6]. It is conceivable that extensive hepatic resection, including the region of latent intrahepatic metastasis, is essential to prevent postoperative recurrence of HCC [14]. In most cases, however, the scope of hepatic resection is often restricted due to preexisting chronic liver disease. As a result, adjuvant treatments such as chemoembolization (TAE), percutaneous ethanol injection (PEI), and arterial infusion chemotherapy (AI) have been applied to improve the postoperative results in HCC cases [10, 12, 15].

In addition to capsular invasion, vascular invasion and intrahepatic metastasis, which had been regarded as the risk factors for postoperative recurrence of HCC [1], indices utilizing molecular biology such as DNA histograms and the bromodeoxyuridine labeling index have recently gained attention [13, 14]. Concerning the histological evaluation, microscopic morphometric analysis, introduced by Motohashi et al. [9], enables us to quantify the grade of atypism. Therefore, we evaluated the relationship between the morphometric indices of atypism and the postoperative survival rates of HCC patients.

Patients and methods

Of 116 cases of HCC treated by hepatic resection at Aichi Medical University during the last 15 years and 7 months, 84 cases, including 55 with associated liver cirrhosis, were retrospectively analyzed (Table 1). The gross findings were classified according to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer in Japan [6, 8].

The resected specimens of HCC were fixed in 10% formalin and cut into 5-μm slices. These thin slices were stained with hematoxylin-eosin for micromorphometric study using an image analyzer (Excel Image Command 4198; Ratoc System Engineering Co., Ltd.). The mean values of the cell area (μm^2), the nuclear area, the nucleocytoplasmic ratio (N/C), and the nuclear form factor (NFF) and its

Table 1. Stage and Procedure in Patients with Hepatocellular Carcinoma

	cirrhotic	non-cirrhotic	totals
Stage I	7	1	8
Stage II	23	9	32
Stage III	15	13	28
Stage IV	10	6	16
totals	55	29	84

	Stage I	Stage II	Stage III	Stage IV	totals
absolute curative	6				6
relative curative	2	22	14		38
relative noncurative		10	13	3	26
absolute noncurative			1	13	14
totals	8	32	28	16	84

Table 2. Morphometry of Hepatocellular Carcinoma

Cell Area (CA; μm^2)
Nuclear Area (NA; μm^2)
Nucleo-cytoplasmic Ratio (N/C)
Nuclear Form Factor (NFF; $4\pi NA/(\text{nuclear circumference})^2$)
Coefficient of Variance of NFF (NCV; %)

coefficient of variance (NCV, %) of the predominant focus of cancer cells were measured for each case (Table 2). For each morphometric index, the 84 cases were separated into 2 groups according to cell differentiation [9]. The cumulative survival rates were compared with each other by the Kaplan-Meier method and the log-rank test. Correlations among the morphometric indices and the gross findings were analyzed by the chi-square test.

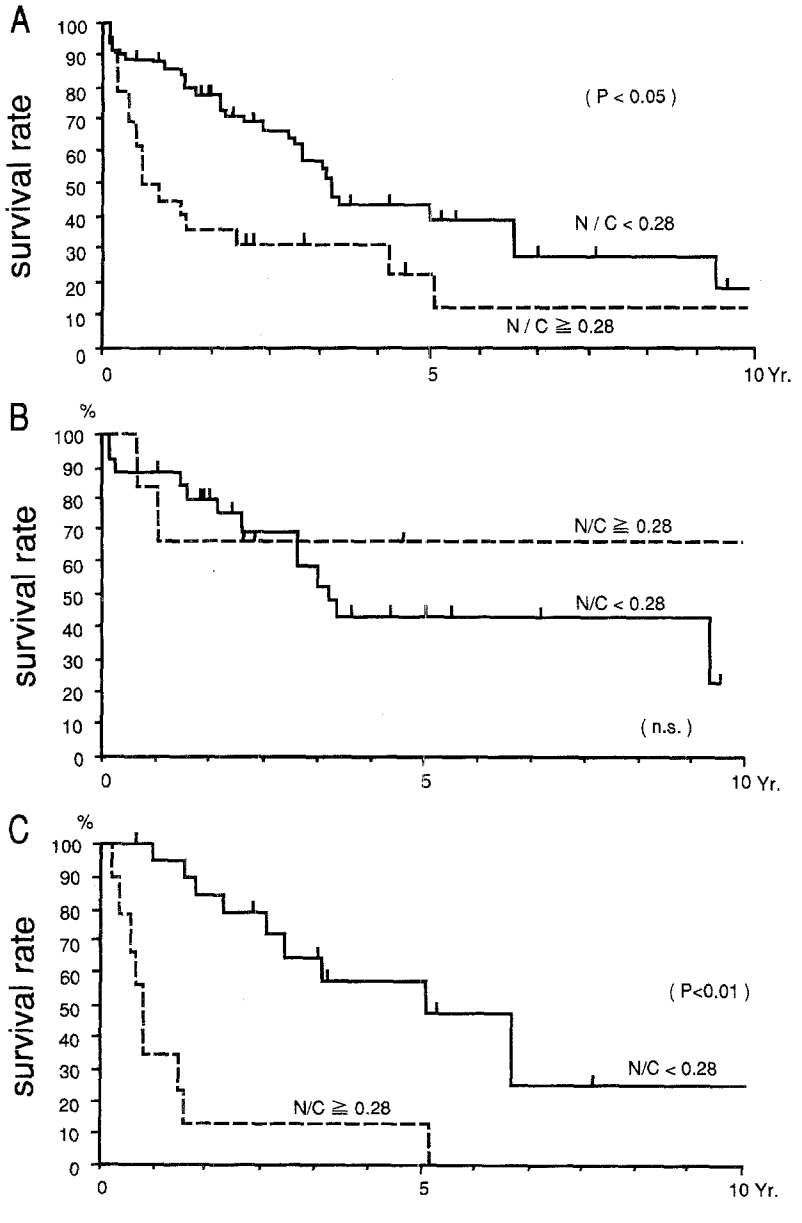

Fig. 1 A–C. Cumulative survival curves after hepatectomy (Kaplan-Meier). **A** All resected cases. **B** Stage II cases. **C** Stage III cases

Table 3. N/C distribution in each grade of portal vein invasion

	VP_0	VP_1	VP_2	VP_3	totals
N/C <0.28	49	5	5	1	60
N/C ≥0.28	9	9	3	3	24
totals	58	14	8	4	84
					P <0.001

Table 4. N/C distribution in each grade of intrahepatic metastasis

	IM_0	IM_1	IM_2	IM_3	totals
N/C <0.28	37	9	11	3	60
N/C ≥0.28	8	4	5	7	24
totals	45	13	16	10	84
					P <0.05

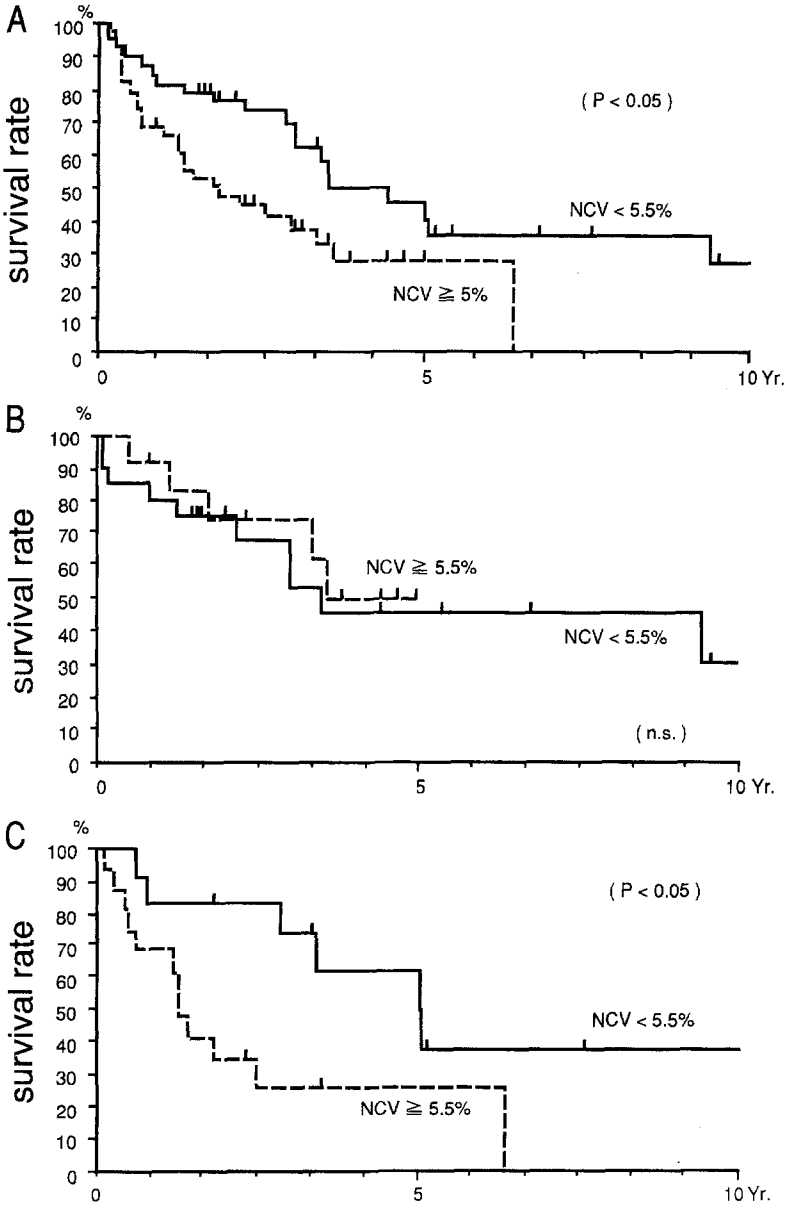

Fig. 2A–C. Cumulative survival curves after hepatectomy (Kaplan-Meier). **A** All resected cases. **B** Stage II cases. **C** Stage III cases

Results

The mean survival time of 58 months for cases with an N/C of less than 0.28 was significantly longer than the 38 months for cases with an N/C of 0.28 or more (P <0.05). In stage II disease, the mean survival times were 63 months for cases with an N/C of less than 0.28 and 121 months for cases with an N/C of 0.28 or more. The difference was not significant. In stage III disease, the mean survival time of 63 months for cases with an N/C of less than 0.28 was significantly longer than the 13 months for cases with an N/C of 0.28 or more (P <0.01, Fig. 1).

The mean survival time of 71 months for cases with an NCV of less than 5.5 was significantly longer than the 33 months for cases with an NCV of 5.5 or more (P <0.05). In stage II disease, the mean survival times were 81 months for cases with an NCV of less than 5.5 and 43 months for cases with an NCV of 5.5 or more; the difference was not significant. In stage III disease, shown at the bottom of Fig. 2, the mean survival time of 69 months for cases with

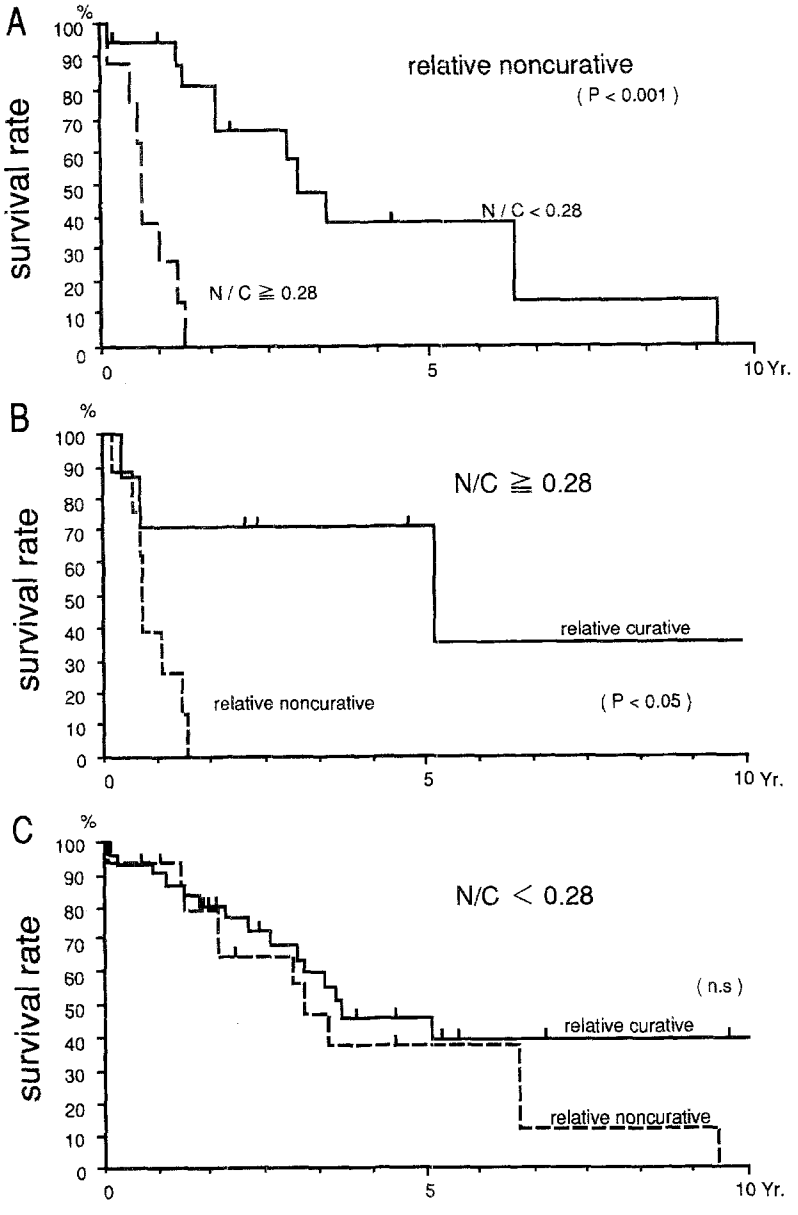

Fig. 3A–C. Cumulative survival curves after hepatectomy (Kaplan-Meier). **A** Cases treated by relative noncurative hepatectomy. **B** Cases with an N/C of 0.28 or more. **C** Cases with an N/C of less than 0.28

an NCV of less than 5.5 was significantly longer than the 29 months for cases with an NCV of 5.5 or more (P <0.05).

In relation to vascular invasion, of the cases with an N/C of less than 0.28, only 18% had portal vein invasion, whereas 62% of those with an N/C of 0.28 or more had portal vein invasion (P <0.001). Regarding intrahepatic metastasis, only 38% of cases with an N/C of less than 0.28 had intrahepatic metastases, whereas 67% of those with an N/C of 0.28 or more had intrahepatic metastases (P <0.05, Tables 3, 4).

Among the cases treated by relative curative resection, the mean survival times were 66 months for cases with an N/C of less than 0.28 and 86 months for cases with an N/C of 0.28 or more; the difference was not significant. The mean survival time of 49 months for cases with an N/C of less than 0.28 was significantly longer than the 8 months for cases with an N/C of 0.28 or more (P <0.001, Fig. 3A). Among the patients with an N/C of 0.28 or more, the mean survival time of 86 months in cases treated by relative curative hepatectomy was significantly longer than the 8 months recorded for cases treated by relative noncurative hepatectomy (P <0.05, Fig. 3B). Among the patients with an N/C of less than 0.28, the mean survival times were 66 months for cases treated by relative curative hepatectomy and 49 months for cases treated by relative noncurative hepatectomy; the difference was not significant (Fig. 3C).

Discussion

Pathological classification according to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer in Japan [8] was decided on the basis of the report by Edmondson and Steiner [2] and its modification [7]. Because the frequeny of detection of small liver cancers has increased due to recent progress in diagnostic modalities, some objective and quantitative indices are required to

differentiate "early liver cancer" from nonneoplastic nodules [9]. Clinicopathological analysis and molecular biological analysis pointed out correlations among the histopathological atypism of HCC, the clinicopathological findings, and the cell proliferation kinetics [3].

In the present study, microscopic morphometric analysis was applied to the operative findings and the outcomes of cases of HCC treated by hepatic resection. N/C and NCV were suggested to be useful prognostic factors in relation to the grade of vascular invasion and intrahepatic metastasis. These trends were remarkable in the stage III cases and the cases treated by relative noncurative hepatic resection. To improve the postoperative results in relation to N/C, extended, curative hepatic resection should be applied for patients with an N/C of 0.28 or more, and adjuvant therapeutic modalities such as arterial infusion chemotherapy combined with Lipiodol should be used when patients are treated by relative noncurative hepatic resection.

Many factors, such as vascular invasion, intrahepatic metastasis, histological atypism, the DNA ploidy pattern, and the bromodeoxyuridine labeling index, were observed to affect the prognosis after hepatic resection [4, 13]. Although extended or curative hepatic resection should be performed to improve the survival rate, many cases have been treated by limited or relative noncurative hepatic resection because of poor liver functional reserve due to preexisting liver cirrhosis [14]. Our experience has confirmed the value of gross clinicopathological findings according to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer in Japan as prognostic factors [5, 11]. In relation to these factors, the microscopic morphometric indices were demonstrated to be important prognostic factors that can be utilized in making decisions regarding the operative procedure and adjuvant therapy.

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