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Potentially Multicentric Hepatocellular Carcinoma: Clinicopathologic Characteristics and Postoperative Prognosis

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Abstract. When multiple hepatic tumors are present, it is sometimes difficult to distinguish between metastatic and multicentric hepatocellular carcinoma (HCC). To identify the important clinicopathologic features of multicentric HCC, we evaluated the clinical characteristics of patients with multicentric HCC and examined the usefulness of surgical treatment in those patients. A total of 99 patients with multiple HCCs were classified into one of the following two groups according to whether their tumors were multicentric or metastatic: Group MO consisted of 18 patients with tumors thought to have developed synchronously from multicentric origins. Group IM consisted of 64 patients with intrahepatic metastases. In this study 18% of the patients with multiple HCCs were thought to have presented with multicentric tumors. This study revealed that synchronous multicentric HCCs often affected multiple segments of the liver and responded relatively well to partial hepatectomy of individual tumor-affected areas. To appropriately treat potentially multicentric HCC, it is important to understand the histopathologic characteristics of multicentric HCC and diagnose during preoperative and intraoperative ultrasonography, so surgical treatment may be useful.

Multiple cancer nodules of hepatocellular carcinoma (HCC) are frequently detected in the liver following careful clinical or pathologic examination [1, 2]. When there are multiple HCC lesions, whether such cases are classified as a primary tumor with intrahepatic metastases or as multicentric tumors, it is an important problem in the staging and treatment of these patients. The multistep development of HCC, from an early to an advanced stage, has been studied histopathologically [3, 4]. The coexistence of atypical adenomatous hyperplasia (AH) and HCC in a cirrhotic liver and the presence of multiple atypical AH, is consistent with the theory of multistep, multicentric development of HCC [5, 6]. These findings suggest that about one-half of atypical AH or HCC may be of multicentric origin and one-half of unicentric origin [7]. It should be noted here that "de novo" carcinomas, those without histologic stepwise development, are known to exist [8]. Because of the difficulty of the differential diagnosis, from a histologic view point the uni- or multicentric origin of atypical AH or HCC has not been evaluated. In this study, we classified all multiple HCCs resected at our department by their mode of development. In addition, patients with potentially multicentric HCCs were evaluated according to their clinicopathologic characteristics and their postoperative survival, and the usefulness of surgical treatment in those patients was examined.

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Materials and Methods

Patients

Among the 376 patients with HCC who underwent resections at our department between January 1981 and July 1995, those who died following surgery and those who underwent absolutely noncurative resections were excluded. There were 99 patients who had two or more lesions detected at their initial surgery. The 99 patients with multiple HCC consisted of 85 men and 14 women ranging in age from 21 to 74 years (mean 58 years). The causes of death in this group included cancer (n = 36), hepatic failure (n = 7), and gastrointestinal bleeding (n = 1). Excluding 17 patients with tumors too difficult to classify, the patients were subdivided into one of the following two groups: group MO, patients with tumors thought to have developed synchronously from multicentric origins (n = 18); and group IM, patients with multiple tumors due to intrahepatic metastases (n = 64). An unclassified group (n = 17) included those where one nodule was moderately differentiated HCC and another nodule was moderately or poorly differentiated HCC. To study the usefulness of hepatectomy in group MO, we assigned 11 patients from this group who underwent partial hepatectomy to remove each nodal tumor to group MO Hr0. Of the 197 cases of solitary HCC, stage I cases treated by partial hepatectomy were assigned to group S-St I Hr0 (n = 34), and stage II cases treated by partial hepatectomy were assigned to group S-St II Hr0 (n = 50). The stages of the remaining 113 patients with solitary HCC included stage I cases (n = 12), stage II cases (n = 79), and stage III cases (n = 22). Postoperative survival rates were compared among the MO Hr0, S-St I Hr0, and S-St II Hr0 groups.

Pathologic Examination

The resected liver specimens were fixed in 10% formalin and embedded in paraffin. For microscopic examination, the sections were stained with hematoxylin and eosin. All diagnoses, including

Table 1. Clinical features of group with multicentric tumors (n = 18).

Feature	Result
Age (year)	57.1 ± 7.1
Sex (M/F)	16/2
Liver cirrhosis	17/18 (94%)
HBsAg-positive	11/18 (61%)
HCVAb-positive	5/18 (28%)
K_{ICG} (min^{-1})	0.12 ± 0.04
Tumor size (cm)	3.3 ± 2.0
Tumor site	
One segment	4
Two or more segments	14
Operative procedure	
Partial resection	11
Subsegmentectomy	2
Segmentectomy	3
Bisegmentectomy	2
Histologic grade of differentiation (main nodule)	
Well differentiated	6
Moderately differentiated	10
Poorly differentiated	2
Histologic fatty change	11/18 (61%)
Adenomatous hyperplasia	6/18 (33%)

Data are expressed as mean ± SD. HBsAg: hepatitis B surface antigen; HCVAb: hepatitis C virus antibody; K_{ICG}: plasma clearance rate of indocyanin green.

histopathologic diagnoses, were based primarily on the General Rules of the Clinical and Pathological Study of Primary Liver Cancer in Japan [9], although in some cases other criteria were used [3, 10].

Criteria

The General Rules for Clinical and Pathological Studies on Liver Cancer define the following multiple HCCs as primary tumors with intrahepatic metastases (IMs): (1) tumors that appear to have developed from or on the basis of portal tumor emboli; (2) tumors that are distributed in a gradient-like pattern (i.e., clustered more densely around the largest lesion and more sparsely farther from it); or (3) tumors that have separate tumors located near the largest lesion, clearly smaller than the largest lesion, and histologically similar or less differentiated than the largest lesion. In this study, lesions consistent with any of these criteria were regarded as IMs of HCC.

On the other hand, we attempted to define a multicentric occurrence of HCC according to the histopathologic diagnosis in the resected liver sections. Lesions were regarded as synchronous multicentric tumors (MO) when: (1) there were multiple nodules of well differentiated carcinoma; (2) nodules of well differentiated carcinoma were concurrent with larger nodules of moderately or poorly differentiated carcinoma; or (3) well differentiated carcinomatous tissues were observed in the margin of moderately or poorly differentiated carcinomatous tissues in multiple or simultaneously occurring nodules, and when the absence of vascular involvement suggested a multicentric origin of the tumors.

Statistical Analysis

The survival rates and recurrence-free survival rates were calculated using Kaplan and Meier's method [11], and the survival curves were compared using the generalized Wilcoxon test [12].

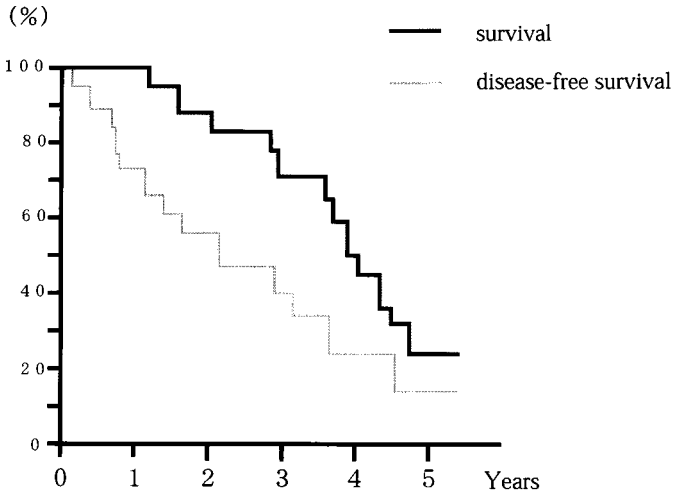

Fig. 1. Cumulative survival rates and disease-free survival rates of group MO patients.

All results are expressed as the mean ± SD. Comparison between items was made by the unpaired Student's t-test. The frequency of each characteristic of the HCCs was also analyzed by the chi-square test. A p value of less than 0.05 was considered significant.

Results

Clinicopathologic Features of Synchronous Multicentric HCC

Clinical features of patients in group MO are summarized in Table 1. The maximum tumor diameter was 3.3 ± 2.0 cm; it was 3.0 cm or less in 11 cases. The tumor affected only one segment in 4 cases and two or more segments in 14 cases. Partial hepatectomy of two or more narrow segments was performed in 11 cases. Adenomatous hyperplasia was seen in 6 of these 18 cases (33%).

Postoperative Survival of Patients with Synchronous Multicentric HCC

The 3-year cumulative survival rate of the patients in group MO was 70% (Fig. 1). On the other hand, the 3-year disease-free survival rate of the patients in group MO was 39% (Fig. 1).

For those in group MO, recurrences in the remnant liver were detected in 11 (61%). The site of recurrence in the remnant liver was the same segment as the initial lesion alone in only one case, another segment alone in five, and both the same segment and other segments in five.

Comparison of Background Factors between Patients of MO Hr0 and Patients of S-St I Hr0 and S-St II Hr0

Clinical features of the patients between MO Hr0 and S-St I Hr0 and S-St II Hr0 are summarized in Table 2. No difference was observed in the age, sex, frequency of liver cirrhosis, positive rates of hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (HCVAb), or K_{ICG} (min^{-1}).

Table 2. Background factors comparing MO Hr0 with S-St I Hr0 and MO Hr0 with S-St II Hr0.*

Factor	MO Hr0 (n = 11)	S-St I Hr0 (n = 34)	S-St II Hr0 (n = 50)
Age	58.4 ± 6.3	57.0 ± 9.1	60.0 ± 9.8
Sex (M/F)	10/1	26/8	42/8
Liver cirrhosis	11/11 (100%)	33/34 (97%)	48/50 (96%)
HBsAg-positive	6/11 (55%)	12/34 (35%)	15/50 (30%)
HCVAb-positive	4/11 (36%)	8/34 (24%)	13/50 (26%)
K_{ICG} (min^{-1})	0.12 ± 0.04	0.12 ± 0.05	0.12 ± 0.04

MO: multicentric tumors; Hr0: partial hepatectomy to remove nodal tumor; S-St I Hr0: stage I cases treated by partial hepatectomy; S-St II Hr0: stage II cases treated by partial hepatectomy.

*MO Hr0 vs. S-St I Hr0; MO Hr0 vs. S-St II Hr0: no statistically significant difference was found.

Comparison of Survival after Partial Hepatectomy Between Patients of MO Hr0 and Patients of S-St I Hr0 or S-St II Hr0

Although the tumor stage at the time of surgery was often higher in MO Hr0 patients than in patients with solitary HCC, the postoperative survival rate did not differ between these two groups (Fig. 2).

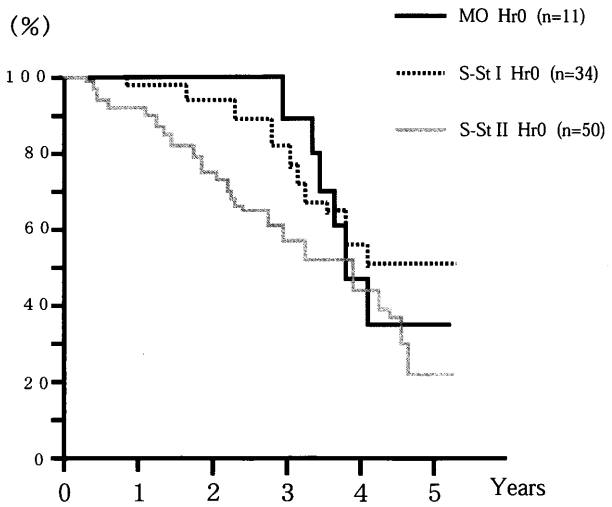

Fig. 2. Comparison of cumulative survival rates between MO Hr0 and S-St I Hr0 and S-St II Hr0. No statistical difference was observed between MO Hr0 and S-St I Hr0 or between MO Hr0 and S-St II Hr0.

Discussion

Hepatocellular carcinoma is complicated by liver cirrhosis and often forms multiple lesions [1, 2, 13], which result in a low resectability rate [13, 14]. Whether these multiple HCC tumors have developed from multicentric origins or are intrahepatic metastases is an important problem when studying and treating this disease. Molecular biology techniques have suggested that a certain proportion of HCCs have multicentric origins by analysis of the integration pattern of HBV DNA [5, 15, 16], analysis of the *p53* mutation patterns [6, 17], the loss of heterozygosity of chromosomal DNA [18], and the DNA ploidy pattern [19]. However, tumor tissues in the nodules of HCC are often heterogeneous, and the conclusions drawn from the application of these molecular biology techniques remain controversial owing to various technical problems including sampling errors. These problems must be resolved in the future.

Because of the recent increase in the number of resected, small HCCs, it has been possible to evaluate the patterns of the growth and spread of HCC. Therefore the theory of a multistep and multicentric origin of HCC has become accepted, and the incidence of potentially multicentric HCC has been increasingly recognized [3–7, 14–24]. Pathologic criteria, based mainly on macroscopic and histologic observations, have been proposed for the differential diagnosis of multiple HCC. Tsuda et al. have considered (1) multiple lesions of early HCC; (2) concurrent early and advanced HCC; and (3) lesions clearly different in histologic profile (degrees of differentiation and atypism) to have developed from multicentric origins, as the metastasis of early HCC is highly unlikely [18]. Furthermore, the Rules for Clinical and Pathological Studies on Liver Cancer [9] strongly suggest that completely well differentiated HCC and HCCs in which well-differentiated cancer tissues are observed in the margin of moderately or poorly differentiated cancer tissues are multicentric. In addition, they stressed that less well differentiated HCC nodules, with a gradual transition to the marginal rim of well differentiated elements, are probably not metastatic tumors. By combining these previous descriptions in this study, we attempted to define multiple HCC as synchronous multicentric tumors (MO) by a number of criteria in addition to the absence of vascular involvement histopathologically.

When treating multiple HCC, percutaneous ethanol injection therapy [25, 26], transcatheter arterial embolization [27, 28], and hepatic arterial infusion therapy [29] are often used because the tumor stage is usually advanced, even when hepatic reserves are relatively poor [30]. Hepatectomy is indicated in only a small percentage of cases of multiple HCC. A proportion of multicentric HCCs appear to be hyperechoic because of marked fatty change. As a result, it is predicted that the emergence of HCC is either multicentric or unicentric during preoperative and intraoperative ultrasonography [21, 31]. In our study, because the postoperative prognosis after hepatectomy was relatively favorable in some patients with multicentric HCC, it seems necessary to review the current criteria for determining the indications for surgery in patients with multicentric HCC. According to one study, the results of partial hepatectomy for treating solitary well differentiated HCC were favorable compared to the results of hepatectomy carried out on the other type of HCC [32]. In patients with synchronous multicentric HCC, diagnosed based on our criteria, well differentiated HCC lesions were often seen among the nodal lesions. According to the General Rules for Surgical and Pathological Studies on Liver Cancer [9], patients at stage II or higher are indicated for partial hepatectomy. In our cases of multicentric HCC, individual nodal tumors appear to be at stage I or II. When we compared the results of partial hepatectomy in patients with synchronous multicentric HCC and the results of partial hepatectomy carried out during the same period in patients with solitary HCC, the postoperative survival rate was comparable between the two groups. The 3-year disease-free survival rate of group MO patients was 39% in our study, indicating that hepatectomy is useful for treating patients allocated to group MO.

We expect that the clinical studies of potentially multicentric HCC will advance, aided by an objective diagnosis as well as by advances in molecular biology methods, in conjunction with the

existing pathologic criteria. In brief, the results of this study suggest that synchronous multicentric HCC often affects multiple segments of the liver and responds relatively well to partial hepatectomy of individual tumor-affected areas. To promote the adequate treatment of potentially multicentric HCC, it is important to understand its histopathologic characteristics, so surgical treatment is effective.

Résumé

En présence de tumeurs hépatiques multiples, il est parfois difficile de faire la différence entre des métastases et un carcinome hépatocellulaire multicentrique. Pour identifier les caractéristiques clinico-pathologiques importantes du carcinome hépatocellulaire, nous avons évalué l'utilité du traitement chirurgical chez ces patients. 99 patients au total, ayant un carcinome hépatocellulaire multiple, ont été classés dans un des groupes suivants selon que la tumeur était multicentrique ou métastatique. Le groupe MO était composé de 18 patients ayant une tumeur supposée être une tumeur synchrone d'origine multiple. Le groupe IM était composé de 64 patients ayant des métastases intrahépatiques. Dans cette étude, on a estimé à 18% le pourcentage de patients ayant un carcinome hépatocellulaire multiple. Cette étude a révélé que le carcinome hépatocellulaire multiple synchrone intéresse souvent des segments multiples du foie et répond relativement bien à une hépatectomie partielle des zones tumorales. Pour traiter de façon correctement une tumeur supposée être un carcinome hépatocellulaire multiple, il est extrêmement important de comprendre les caractéristiques histo-pathologiques du carcinome hépatocellulaire multiple et de bien diagnostiquer ces tumeurs en pré- et en per opératoire, afin de leur opposer un traitement chirurgical utile adapté.

Resumen

En presencia de múltiples tumores hepáticos, en ocasiones se hace difícil diferenciar entre un carcinoma hepatocelular metastásico y uno multicéntrico. Con el fin de identificar las características más importantes del carcinoma hepatocelular multicéntrico, nos propusimos evaluar las características clínicas de pacientes con carcinoma hepatocelular multicéntrico y analizamos la utilidad de practicar tratamiento quirúrgico con ellos. Noventa y nueve pacientes con carcinomas hepatocelulares múltiples fueron clasificados en uno de los siguientes grupos según sus tumores fueran multicéntricos o metastásicos: el Grupo MO consistió en 18 pacientes con tumores considerados como de desarrollo sincrónico a partir de orígenes multicéntricos. El Grupo IM consistió en 64 pacientes con metástasis intrahepáticas. En el presente estudio se consideró que 18% de los pacientes con carcinomas hepatocelulares múltip les se presentaron con tumores multicéntricos. El estudio revela que el CHC multicéntrico sincrónico afecta frecuentemente múltiples segmentos del hígado y responde relativamente bien a la hepatectomía parcial para resecar áreas individuales afectadas por el tumor. Para tratar en forma apropiada un carcinoma hepatocelular multicéntrico es de extrema importancia comprender las características histopatológicas del carcinoma hepatocelular multicéntrico y diagnosticarlo en el curso de la ultrasonografía preoperatoria e intraoperatoria, a fin de que el tratamiento quirúrgico resulte verdaderamente útil.

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Invited Commentary

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The dismal outcome of hepatocellular carcinoma (HCC) even after tumor resection has long been thought to be due to its multicentric origin, leading to a pessimistic view and an inactive therapeutic strategy. The problem of a multicentric or unicentric origin of HCC has been debated for decades. Popper and Schaffner mentioned in 1957 that "carcinomas developing in cirrhotic livers usually seem to be multicentric, while in noncirrhotic livers they are unicentric" [1]. Peters was also of the opinion that both unicentric and multicentric genesis may occur [2]. Cameron favored the opinion that venous invasion seems to be responsible for the multinodular appearance of many liver cancers [3]. Nakashima noted that it cannot be denied that even a cirrhotic liver would develop HCC unicentrically [4]. According to the operative findings and long-term follow-up study of HCC patients with concomitant cirrhosis, we have emphasized the role of a unicentric origin in subclinical HCC, particularly in patients with long-term survival after resection [5]. With the advances of molecular biology since the late 1980s, more and more evidence showed that both multicentric and unicentric origins exist. Several methods have been employed for studies on cell origin: (1) Analyses of the integration pattern of hepatitis B virus DNA, of both unicentric and multicentric origin, were demonstrated in recurrent lesions and multiple HCC nodules [6–8]. (2) The loss of heterozygosity (LOH) pattern on chromosome 16 was claimed useful for diagnosing multifocal HCC [9]. (3) The *p53* LOH has also been employed to identify the clonal origin of recurrent HCC [10, 11]. Based on analysis of small HCCs (<1 cm) found in livers removed at transplantation, different phases were observed proceeding from cirrhotic nodule, hyperplasia, atypical hyperplasia, and well differentiated HCC, suggesting a multicentric origin of recurrence after local excision of small HCCs [12].

In the past it was universally accepted that patients with multinodular HCC had a poorer prognosis than those with a single nodule HCC; the 5-year survivals were 8.0% (n = 274) versus 35.8% (n = 283) in the author's institution. Even for small HCC resections the 5-year survivals were 44.6% versus 76.6% [13].

Yasui et al. found in the present study that the postoperative survival rate did not differ between synchronous multicentric HCC and solitary stages I and II HCC. This encouraging result indicates that even with multinodular HCC aggressive surgery is advocated, particularly in patients with potentially multicentric HCC. Unfortunately, based on data available in the literature, most multinodular HCCs result from intraportal spreading from the "unicentric origin," with synchronous multicentric origin accounting for only 18 of 99 patients with multiple HCCs. Furthermore, parameters for accurately distinguishing between HCCs of unicentric and multicentric origin remained a goal to be studied. Such approaches, including HBV-DNA, *p53* mutation, and LOH pattern of chromosome, were not sufficient to solve the problem. For example, the HBV-DNA integration pattern was not helpful for patients with HCV infection. Therefore the pathologic criteria for synchronous multicentric origin mentioned in this paper is still of value until a better marker appears.

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