Natural History and Prognosis of Adenomatous Hyperplasia and Early Hepatocellular Carcinoma: Multi-institutional Analysis of 53 Nodules Followed Up for More Than 6 Months and 141 Patients with Single Early Hepatocellular Carcinoma Treated by Surgical Resection or Percutaneous Ethanol Injection

Michiie Sakamoto and Setsuo Hirohashi

Pathology Division, National Cancer Center Research Institute, Tokyo, Japan

Background: The natural history and posttherapeutic outcome of adenomatous hyperplasia and early hepatocellular carcinoma have rarely been analyzed.

Methods: Fifty-three hepatic tumors diagnosed as adenomatous hyperplasia or early hepatocellular carcinoma and followed up for more than 6 months and 141 patients with single early hepatocellular carcinoma treated by surgical resection or ethanol injection were collected retrospectively and analyzed.

Results: Some of the adenomatous hyperplasias developed to early and to advanced hepatocellular carcinoma. Tumors tended to grow faster in the order adenomatous hyperplasia, early hepatocellular carcinoma and advanced hepatocellular carcinoma, with respective mean (SD) tumor volume doubling times of 21.2 (10.7), 13.9 (11.7) and 6.0 (5.2) months. Overall survival rates at 5 years in 53 patients treated by surgery and 88 patients treated by ethanol injection were 89.6 and 71.9%, respectively.

Conclusion: Progression of adenomatous hyperplasia and early HCC was confirmed pathologically. Early HCC was shown to have a good prognosis.

Key words: hepatocellular carcinoma – adenomatous hyperplasia – tumor progression – prognosis

INTRODUCTION

Hepatocellular carcinoma (HCC) in countries where it is endemic is strongly associated with chronic infection with hepatitis viruses. Close follow-up of high-risk patients and advances in imaging techniques have made it possible to find HCC at an early stage or equivocal nodular lesions without the features of classical HCC. Histopathological and molecular biological analyses of these lesions have revealed a type of hypercellular lesion known as adenomatous hyperplasia (AH), which lacks structural atypia and cannot be identified as malignant morphologically and is thought to be a precancerous lesion. Early HCC in which the pre-existing liver structure is fairly well preserved within the nodule is considered to correspond to in situ or microinvasive HCC and nodule-in-nodule type HCC composed of progressed HCC within an early HCC is considered to be a transitional form between early and advanced HCC (1–6).

Clinicopathological studies have also indicated malignant transformation of AH (7) and progression of early HCC through a nodule-in-nodule lesion shown by the appearance of a hypervascular nodule within an early HCC (8,9). Based on this understanding of early hepatocarcinogenesis, an increased number of small HCCs have been detected and treated clinically. At present percutaneous ethanol injection and surgical resection are the main treatments for small HCCs (10,11). However, it is still unclear what type of lesion should be treated and when treatment should be started, owing to the lack of extensive analysis of the natural history and prognosis of AH and early HCC.

In this study we retrospectively collected cases of AH or early HCC followed up for more than 6 months to clarify their natural history and treated cases of single early HCC to clarify their prognosis.

MATERIALS AND METHODS

CRITERIA FOR CLASSIFICATION OF SMALL NODULAR LESIONS

Pathological diagnosis was made according to the criteria described previously (1,4). Both early HCC and AH show preservation of pre-existing liver structure within the nodule and...
do not form definite cancerous nodules macroscopically (Fig. 1). Microscopically early HCC contains Glisson’s components including the bile duct and portal vein, corresponding to its macroscopic features and is thought to correspond in situ or microinvasive carcinoma. It is a hypercellular lesion (usually with more than twice the cellularity of the non-tumorous liver) with structural atypia such as abnormal cord structures or formation of acini and mostly with little cell atypia (Edmondson grade I) (Fig. 1). AH is also a hypercellular lesion but lacks structural atypia and cannot be identified as malignant morphologically (Fig. 1). Advanced HCC appears as a definite cancerous nodule with expansive or invasive growth. The terminology of the International Working Party (12) states that some small and well differentiated HCCs have features of early HCC preserving Glisson’s sheath, but recommends that the term ‘early HCC’ be avoided. However, we prefer our own classification because it matches the angiographic features fairly well, i.e. early HCC usually has a portal supply without tumor staining, whereas advanced HCC including small and well differentiated HCC shows tumor staining without portal flow (13). AH is considered to be almost equivalent to the dysplastic nodule defined by the International Working Party. In the case of biopsy specimens, especially from well differentiated HCC, histological information is insufficient for differentiating early from advanced HCC. Therefore, in this study we combined angiographic data with histological information and defined early HCC as well differentiated HCC (Edmondson’s grade I or grade I with a minor component of grade II) negative for tumor staining and advanced HCC as that with tumor staining in angiographic examination.

CASES AND FOLLOW-UP

Fifty-three hepatic tumors diagnosed clinically as AH or early HCC and followed up for more than 6 months in 45 patients were collected from nine institutions and analyzed. The mean age of the patients at initial diagnosis was 63 years and the male:female ratio was 3.9:1.0. All the tumors were examined histologically by needle biopsy or surgical resection at least once during follow-up. Tumors were examined clinically by ultrasonography (US), computed tomography or other modalities. In order to monitor tumor size, maximum tumor diameter determined by US was analyzed. The tumor volume doubling time (TVDT) was calculated as \( t = \frac{t_{div}}{10 \log d - \log d_0} \), where the nodular diameter increased from \( d_0 \) to \( d \) in \( t \) days (14).

Next, 141 patients with single early HCC treated by surgical resection or ethanol injection were studied. Fifty-three patients (group A) underwent hepatectomy and were diagnosed to have a single early HCC both clinically and pathologically. The other 88 (group B) were clinically diagnosed as having a single tumor which was revealed to be early HCC by needle biopsy based on the criteria described above and underwent percutaneous ethanol injection. The mean age of the patients at initial treatment and the male:female ratio were 59 and 1.8 in group A and 64 and 1.7 in group B, respectively. All the patients were followed up and recurrence of HCC was diagnosed either by histological examination or typical CT and/or angiographic findings, or was based on a markedly elevated serum \( \alpha \)-fetoprotein level along with a space-occupying lesion demonstrated by various imaging techniques. The overall survival rate and recurrence-free survival rate were calculated by the Kaplan–Meier method (15).
RESULTS

NATURAL HISTORY OF ADENOMATOUS HYPERPLASIA AND EARLY HCC

Changes in tumor size and pathological diagnosis of 53 tumors followed up more than 6 months are summarized in Fig. 2. Most of the tumors grew larger during their follow-up and their growth rate accelerated in some cases, suggesting tumor progression. In some cases tumor progression was confirmed by histological examination. Eighteen tumors were diagnosed as adenomatous hyperplasia by needle biopsy during follow-up, among which 13 tumors and one tumor were shown to progress to early and advanced HCC, respectively, by histological examination. Diagnosis of early HCC by biopsy was made for 12 tumors during follow-up and four tumors were shown to progress to advanced HCC by histological examination.

TVDT of each type of tumor was analyzed by comparing tumor at the time of histological diagnosis and 6 months or as near to 6 months as possible, prior to histological diagnosis. Therefore, TVDT of 15 and six tumors histologically diagnosed as AH and eHCC, respectively, at the start of observation were not evaluated in this study. TVDT of AH was analyzed for five tumors (in the case of repeated histological diagnosis of AH, only the last one diagnosed was analyzed). TVDT of early HCC and advanced HCC was analyzed for 29 and 10 tumors, respectively, in the same manner as AH.

The TVDT ranges for AH, early HCC and advanced HCC were 8.0–37.4, 1.8–49.6 and 1.2–18.4 months, with mean (SD) periods of 21.2 (10.7), 13.9 (11.7) and 6.0 (5.2) months, respectively.

PROGNOSIS OF EARLY HCC

The overall survival and recurrence-free survival curves for patients with single early HCC treated by surgical resection (group A) or ethanol injection (group B) are shown in Fig. 3. The overall survival rate in group A was 100% at 1 year, 97.8% at 3 years, 89.6% at 5 years and 60.6% at 7 years. In contrast, the corresponding recurrence-free survival rates were 92.2, 72.6, 48.3 and 26.9%, respectively. In group B, the respective overall survival rates were 98.8, 87.7, 71.9 and 17.1% and the recurrence-free survival rates were 84.5, 41.1, 27.9 and 20.9%, respectively.

At the time of analysis, eight out of 53 patients in group A and 19 out of 88 patients in group B had died. The causes of death
years after treatment.

Post-therapeutic outcome of early HCC were analyzed retrospectively. To our knowledge, no other study has analyzed such a large number of cases followed up with histological confirmation or treated against single early HCC. It was confirmed histologically that AH develops to early and to advanced HCC in some cases. This is in agreement with the previous follow-up study reporting malignant transformation of AH (7) and molecular biological evidence of subclonal progression of high-grade nodules within early HCC (5,6,8). The incidence of tumor progression was not assessed, because histological examination was not always done systematically in the present cases and many tumors could not be evaluated as to whether they had progressed or not by biopsy or surgical resection.

It is not easy to differentiate AH from eHCC or eHCC from advanced HCC by imaging diagnosis alone, so we focused on histologically confirmed tumors. The difficulty in performing histological examination by repeated biopsies caused some limitations as described above.

TVDT analysis indicated that tumors tended to grow faster in the order AH, early HCC and advanced HCC. Immunohistochemical analysis using the PCNA labeling index has shown a higher proliferative activity in advanced than in early HCC (18), which is also consistent with the present data. However, TVDT of each type of tumor showed wide deviations, indicating the existence of unusual cases such as early HCC showing very slow growth, AH without progression during the observation period or early HCC showing rapid growth and progression to advanced HCC. In the present analysis of TVDT, the type of tumor at the time of histological diagnosis and 6 months prior to it might not be same and we might be underestimating the TVDT of early or advanced HCC, which also might cause a wide deviation of the TVDT of those tumors. It would be very useful for making decisions about treatment and the follow-up schedule if some prediction could be made about whether AH or early HCC nodules would progress rapidly or remain at an early stage.

It has been reported that the diameter and cellularity of AH can predict the time until transformation (7), that AH with reduced portal flow has more potential for transformation (19) and that tumor cells with fatty change in early HCC show less proliferative activity than those without fatty change (20). Further study is needed to evaluate whether these factors are also useful in the present cases and to find other molecular biological, histological and radiological markers for predicting the biological behavior of AH and early HCC.

In HCC patients, multicentric tumor development is not rare (21) and this makes it difficult to assess the prognostic value of each nodule. Therefore, we selected cases of single early HCC at the time of initial treatment for evaluation of prognosis after treatment. The over-all survival rate at 5 years for patients treated by surgical resection (group A) was 89.6% and for those treated by ethanol injection (group B) it was 71.9%; these rates were higher than those for patients with single advanced HCC <2 cm in diameter who underwent hepatectomy at the National Cancer Center Hospital, where the rate was 65% (T. Takayama, et al., unpublished observation). The concept of early HCC is that the lesion corresponds to a relatively early stage of hepatocarcinogenesis.
The authors are grateful to the following for offering their important cases and for valuable discussions: Drs Kojiro Masamichi, Yasuo Majima and Kiyoshi Tanikawa (Kurume University), Drs Masaaki Ebara (Chiba University) and Drs Kazuki Ito (Gifu Medical College), Dr Masahiro Yoshino (National Cancer Center Hospital East), Drs Kunihiro Okuda and Tadatoshi Takayama (Kanazawa University), Drs Yo Sasaki (Osaka Medical Center for Cancer and Cardiovascular Diseases), Dr Hiroaki Kinoshita (Osaka City University), Drs Masashi Unoura and Shuichi Kaneko (Kanazawa University), Dr Kiyoshi Kudo (Kobe City General Hospital), Dr Kiyoshi Takasaki (Tokyo Women's Medical College), Dr Ren Ichihara Yoshino (National Cancer Center Hospital East) and Drs Kenichi Takayasu, Shuichi Okada and Tadatoshi Takayama (Kanazawa University and National Cancer Center Hospital).

Acknowledgments

This work was supported by Grants-in-Aid for Cancer Research (2-2, 5-1 and 8-3) from the Ministry of Health and Welfare, Japan.

References


