Malignant Transformation of Hepatocellular Adenoma: How Frequently Does It Happen?

Introduction

Hepatocellular adenoma is a very rare disease in Japan, and institutions encounter only a limited number of cases. This is one of the reasons for the current skepticism in Japan over whether hepatocellular adenoma can truly undergo malignant transformation to hepatocellular carcinoma. However, hepatocellular adenoma is highly prevalent in Western countries, particularly in Europe, and textbooks from these countries have long noted that hepatocellular adenoma carries risks of bleeding and malignant transformation. Most of the cases of hepatocellular carcinoma routinely encountered in Japan occur as a result of chronic liver injury from viral disease, and it is extremely rare to encounter liver cancer that has developed from hepatocellular adenoma in healthy liver. It would be no exaggeration to say that this is almost never seen. Therefore, a survey and literature review was conducted to assess how many cases of hepatocellular adenoma actually undergo malignant transformation in Japan.

Nationwide Survey in Japan

A nationwide survey was conducted in 1000 institutions, mainly those participating in follow-up surveys conducted by the Liver Cancer Study Group of Japan. Valid responses were obtained from only 56 institutions. Of these, 38 had encountered hepatocellular adenoma and 18 had not. The total number of cases encountered was 63. Treatment was resection [1] in 40 cases, transcatheter arterial chemoembolization [2] in 2 cases, and careful follow-up in 21 cases. The ways in which diagnosis came about were as follows: tumor rupture (n = 4), incidental detection on screening (n = 25), referral from another hospital or clinic (n = 32), and other (n = 2). Malignant transformation of hepatocellular adenoma was believed to have occurred in only 2 of these 63 cases (3.2%): diagnostic confirmation was made based on tumor growth in one case and on tumor growth together with liver biopsy results in the other. Not even a single case was reported in which malignant transformation of hepatocel-
Liver adenoma was determined to have occurred based on resection showing a hepatocellular carcinoma surrounded by a hepatocellular adenoma. The above results indicate that malignant transformation of hepatocellular adenoma is very rarely observed in a routine clinical setting in Japan (table 1).

**Table 1. Survey results**

| Question                                                                 | Response       | Number  |
|--------------------------------------------------------------------------|---------------|---------|
| 1. Sent to a total of 1000 institutions                                   |               |         |
| 2. Responses received from 56 institutions                               |               |         |
| 3. Has your institution encountered hepatocellular adenoma?              | Yes           | 38 institutions, 63 cases |
|                                                                          | No            | 18 institutions           |
| 4. Treatment method                                                      | Resection     | 40 cases              |
|                                                                          | Transcatheter embolization/chemoembolization | 2 cases |
|                                                                          | Ablation      | 0 cases                |
|                                                                          | Watchful waiting | 21 cases       |
| 5. How the diagnosis was made                                            | Tumor rupture | 4 cases                      |
|                                                                          | Screening     | 25 cases               |
|                                                                          | Referral from another hospital/clinic | 32 cases |
|                                                                          | Other         | 2 cases                |
| 6. In how many cases do you believe malignant transformation of HCA occurred? | Two cases (one based on tumor growth, one based on tumor growth + liver biopsy) |         |

**Literature Review**

According to an analysis of the literature by Farges et al. that reports at least 20 resected hepatocellular adenomas, hepatocellular carcinoma nodules were clearly observed within hepatocellular adenoma in 3 of 74 patients (5%) in the 1980s, 4 of 136 patients (4%) in the 1990s, and 30 of 530 patients (6%) in the 2000s [3–18] (table 2). Their review included a report of 25 cases of hepatocellular adenoma reported by Ichikawa et al. (the first author worked at a Japanese institution and co-authors worked overseas in the USA and Italy) in which hepatocellular carcinomas were found in 2 of the 14 hepatocellular adenomas resected. However, these could well have been patients at the overseas sites, which would mean that no substantial report of malignant transformation of hepatocellular adenoma in Japanese patients has been published to date. Stoot et al. analyzed 1635 cases of hepatocellular adenoma compiled from 157 articles and 17 case reports published between 1970 and 2010, and found a malignant transformation rate of 4.2% [19]. They reported that among hepatocellular adenomas ≤5 cm in diameter, only 3 (4.2%) underwent malignant transformation. Stoot et al.’s review covers the large studies by Dokmak et al. (n = 122) [18], Deneve et al. (n = 124) [16], and Bioulac-Sage et al. (n = 128) [15], which were also included in the abovementioned review by Farges et al. [20]. The rate of malignant transformation was 10% according to Dokmak et al. [18] and 4% according to both Deneve et al. [16] and Bioulac-Sage et al. [17]. Farges et al. also assessed malignant transformation in 218 resected hepatocellular adenomas based on an abnormal trabecular pattern and a reduced reticulin network or glypican-3 expression, and found a transformation rate of 10% [21]. Among these patients, the risk of malignant transformation was observed to be 4% in women and 47% in
men, with 64% of cases having a β-catenin-activated hepatocellular adenoma. Furthermore, 31% of these patients also had metabolic syndrome. Therefore, Farges et al. concluded that although malignant transformation is not clearly an established disease concept of hepatocellular adenoma, it may not be as rare as was previously thought.

However, Witjes et al. pointed out that because malignant transformation of hepatocellular adenoma is exceedingly rare in non-cirrhotic livers, it is biased to review resected cases only, and as such this rate may be overestimated [22]. They studied 52 hepatocellular carcinomas in 48 patients with non-cirrhotic livers and none of the findings indicated pathological transition from hepatocellular adenoma to hepatocellular carcinoma, and the expression of markers of well-differentiated hepatocellular carcinoma or hepatocellular adenoma was not observed in seven patients. Thus, there was no evidence that the cancer developed from hepatocellular adenoma in any of their cases. Nault et al. have also noted that many reports of malignant transformation of hepatocellular adenoma based on hepatectomy overestimate its incidence [23]. Whether or not hepatocellular adenoma can undergo malignant transformation is one of the most debated aspects of hepatocellular adenoma, and more basic and clinical research must be conducted on this issue.

The 2010 updated edition of the WHO Classification of Tumours of the Digestive System clearly states that β-catenin-activated hepatocellular adenomas are at high risk for malignant transformation to hepatocellular carcinoma [24]. However, malignant transformation of hepatocellular adenoma remains a controversial issue even in Europe and the United States, where there is a much higher incidence of hepatocellular adenoma than in Japan.

### Table 2. Frequency of malignant transformation of hepatocellular adenoma: Number of reported cases by decade from reports including at least 20 resected cases

| Reference (first author) | Publication year | Patients with adenoma | HCC within adenoma number of patients |
|--------------------------|------------------|------------------------|--------------------------------------|
|                          |                  | total                  | resected | sex ratio |
| Kerlin [14]              | 1983             | 23                     | 17       | 21/2     | 2 |
| Mathieu [15]             | 1986             | 27                     | 27       | 27/0     | 0 |
| Leese [16]               | 1988             | 24                     | 17       | 16/8     | 1 |
| Total                    |                  | 74                     | 61       | 3/5 (%)  |
| Arrive [17]              | 1994             | 29                     | 21       | 27/2     | 01 |
| Foster [18]              | 1994             | 50                     | 37       | NA       | 12 |
| Nagorney [19]            | 1995             | 24                     | 19       | 22/2     | 1 |
| Weimann [20]             | 1997             | 44                     | 39       | 39/4     | 2 |
| Total                    |                  | 136                    | 116      | 4/4 (%)  |
| Ichikawa [21]            | 2000             | 25                     | 14       | 21/4     | 2 |
| Reddy [22]               | 2001             | 25                     | 25       | 25/0     | 1 |
| Terkvatan [23]           | 2001             | 33                     | 19       | 29/4     | 0 |
| Toso [24]                | 2005             | 25                     | 25       | 23/2     | 2 |
| Van der Windt [25]       | 2006             | 48                     | 16       | 48/0     | 2 |
| Cho [26]                 | 2008             | 41                     | 41       | 38/3     | 2 |
| Deneve [27]              | 2009             | 124                    | 119      | 116/8    | 5 |
| Bioulac-Sage [11]        | 2009             | 128                    | 128      | 116/12   | 6 |
| Dokmak [12]              | 2009             | 122                    | 122      | 108/14   | 10 |
| Total                    |                  | 530                    | 509      | 30/6 (%) |

1Dysplasia was present in 3 patients. 2Hepatocholangiocarcinoma. Reproduced with permission from Farges O, et al.[20].
Conclusion

There have been no definite reports of hepatocellular adenoma truly undergoing malignant transformation in Japan, where few cases of hepatocellular adenoma are encountered, so this will likely continue to remain a major issue of contention here. To resolve this issue, we have to wait for the results of basic and clinical research conducted in Western countries where the disease is more common. Given that there have been no reports definitively showing hepatocellular adenoma pathologically transitioning to hepatocellular carcinoma, the least that can be said at this time is that malignant transformation of hepatocellular adenoma should not pose much of a problem in routine clinical practice.

However, recent advances in imaging [25, 26] and molecular classification have made it easier to diagnose hepatocellular adenomas and even to subclassify them. Therefore, for the time being, resection remains the first-line treatment for hepatocellular adenoma due to concerns about bleeding risk and the small but present risk of malignant transformation.

References

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