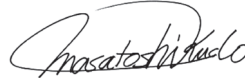


Editorial

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

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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-

Table 1. Survey results

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)	

lular 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).

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

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	0 ¹
Foster [18]	1994	50	37	NA	1 ²
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
Terkivatan [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].

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.

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

- Mise Y, Sakamoto Y, Ishizawa T, Kaneko J, Aoki T, Hasegawa K, Sugawara Y, Kokudo N: A worldwide survey of the current daily practice in liver surgery. *Liver Cancer* 2013;2:55–66.
- Raoul JL, Gilabert M, Piana G: How to define transarterial chemoembolization failure or refractoriness: a European perspective. *Liver Cancer* 2014;3:119–124.
- Kerlin P, Davis GL, McGill DB, Weiland LH, Adson MA, Sheedy PF 2nd: Hepatic adenoma and focal nodular hyperplasia: clinical, pathologic, and radiologic features. *Gastroenterology* 1983;84:994–1002.
- Mathieu D, Bruneton JN, Drouillard J, Pointreau CC, Vasile N: Hepatic adenomas and focal nodular hyperplasia: dynamic CT study. *Radiology* 1986;160:53–58.
- Leese T, Farges O, Bismuth H: Liver cell adenomas. A 12-year surgical experience from a specialist hepatobiliary unit. *Ann Surg* 1988;208:558–564.
- Arrivé L, Fléjou JF, Vilgrain V, Belghiti J, Najmark D, Zins M, Menu Y, Tubiana JM, Nahum H: Hepatic adenoma: MR findings in 51 pathologically proved lesions. *Radiology* 1994;193:507–512.
- Foster JH, Berman MM: The malignant transformation of liver cell adenomas. *Arch Surg* 1994;129:712–717.
- Nagorney DM: Benign hepatic tumors: focal nodular hyperplasia and hepatocellular adenoma. *World J Surg* 1995;19:13–18.
- Weimann A, Ringe B, Klempnauer J, Lamesch P, Gratz KF, Prokop M, Maschek H, Tusch G, Pichlmayr R: Benign liver tumors: differential diagnosis and indications for surgery. *World J Surg* 1997;21:983–990; discussion 990–981.
- Ichikawa T, Federle MP, Grazioli L, Nalesnik M: Hepatocellular adenoma: multiphasic CT and histopathologic findings in 25 patients. *Radiology* 2000;214:861–868.
- Reddy KR, Kligerman S, Levi J, Livingstone A, Molina E, Franceschi D, Badalamenti S, Jeffers L, Tzakis A, Schiff ER: Benign and solid tumors of the liver: relationship to sex, age, size of tumors, and outcome. *Am Surg* 2001;67:173–178.
- Terkivatan T, de Wilt JH, de Man RA, van Rijn RR, Zondervan PE, Tilanus HW, IJzermans JN: Indications and long-term outcome of treatment for benign hepatic tumors: a critical appraisal. *Arch Surg* 2001;136:1033–1038.
- Toso C, Majno P, Andres A, Rubbia-Brandt L, Berney T, Buhler L, Morel P, Mentha G: Management of hepatocellular adenoma: solitary-uncomplicated, multiple and ruptured tumors. *World J Gastroenterol* 2005;11:5691–5695.
- van der Windt DJ, Kok NF, Hussain SM, Zondervan PE, Alwayn IP, de Man RA, IJzermans JN: Case-orientated approach to the management of hepatocellular adenoma. *Br J Surg* 2006;93:1495–1502.
- Cho SW, Marsh JW, Steel J, Holloway SE, Heckman JT, Ochoa ER, Geller DA, Gamblin TC: Surgical management of hepatocellular adenoma: take it or leave it? *Ann Surg Oncol* 2008;15:2795–2803.
- Deneve JL, Pawlik TM, Cunningham S, Clary B, Reddy S, Scoggins CR, Martin RC, D'Angelica M, Staley CA, Choti MA, Jarnagin WR, Schulick RD, Kooby DA: Liver cell adenoma: a multicenter analysis of risk factors for rupture and malignancy. *Ann Surg Oncol* 2009;16:640–648.
- Bioulac-Sage P, Laumonier H, Couchy G, Le Bail B, Sa Cunha A, Rullier A, Laurent C, Blanc JF, Cubel G, Trilaud H, Zucman-Rossi J, Balabaud C, Saric J: Hepatocellular adenoma management and phenotypic classification: the Bordeaux experience. *Hepatology* 2009;50:481–489.
- Dokmak S, Paradis V, Vilgrain V, Sauvanet A, Farges O, Valla D, Bedossa P, Belghiti J: A single-center surgical experience of 122 patients with single and multiple hepatocellular adenomas. *Gastroenterology* 2009;137:1698–1705.

- 19 Stoot JH, Coelen RJ, De Jong MC, Dejong CH: Malignant transformation of hepatocellular adenomas into hepatocellular carcinomas: a systematic review including more than 1600 adenoma cases. *HPB (Oxford)* 2010;12:509–522.
- 20 Farges O, Dokmak S: Malignant transformation of liver adenoma: an analysis of the literature. *Dig Surg* 2010;27:32–38.
- 21 Farges O, Ferreira N, Dokmak S, Belghiti J, Bedossa P, Paradis V: Changing trends in malignant transformation of hepatocellular adenoma. *Gut* 2011;60:85–89.
- 22 Witjes CD, Ten Kate FJ, van Aalten SM, Dwarkasing RS, Willemsen FE, Verhoef C, de Man RA, Ijzermans JN: Hepatocellular adenoma as a risk factor for hepatocellular carcinoma in a non-cirrhotic liver: a plea against. *Gut* 2012;61:1645–1646.
- 23 Nault JC, Bioulac-Sage P, Zucman-Rossi J: Hepatocellular benign tumors – from molecular classification to personalized clinical care. *Gastroenterology* 2013;144:888–902.
- 24 Bioulac-Sage P, Balabaud C, Wanless IR: Focal nodular hyperplasia and hepatocellular adenoma. In: WHO classification of tumours of the digestive system; in Bosman FT, Carneiro F, Hruban RH, Theise ND (eds), ed4. IARC, Lyon, 2010.pp198–204.
- 25 Murakami T, Tsurusaki M: Hypervascular benign and malignant liver tumors that require differentiation from hepatocellular carcinoma: key points of imaging diagnosis. *Liver Cancer* 2014;3:85–96.
- 26 Ichikawa T, Sano K, Morisaka H: Diagnosis of pathologically early HCC with EOB-MRI: experiences and current consensus. *Liver Cancer* 2014;3:97–107.