学 位 論 文 の 要 旨

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学　位　論　文　名　Progression of Hepatic Hypovascular Nodules With Hypointensity in the Hepatobiliary Phase of Gd-EOB-DTPA-enhanced MRI in Hepatocellular Carcinoma Cases

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論 文 内 容 の 要 旨

INTRODUCTION

Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA) is a liver-specific magnetic resonance imaging (MRI) contrast agent. Previous studies have shown Gd-EOB-DTPA-MRI to have a higher sensitivity for detecting hepatocellular carcinoma (HCC) than other imaging modalities. We often observe hypointensity nodules in the hepatobiliary phase of Gd-EOB-DTPA-MRI that are hypovascular in the arterial phase. These tend to be diagnosed as dysplastic nodules or possible well-differentiated HCC, required follow-up examinations. During the follow-up period, some lesions become typical HCCs, while others do not. At present, it is not known which hypovascular nodules detected by Gd-EOB-DTPA-MRI will finally become HCC. Additionally, in patients without a past history of HCC treatment, the natural history of these hypovascular nodules has not yet been investigated.

In this retrospective longitudinal study, we examined the natural course of Gd-EOB-DTPA-MRI-detected hypovascular nodules in patients without a past HCC treatment history. We also analyzed the possible factors related to a future HCC progression from these nodules.

MATERIALS AND METHODS

The study protocol was approved by the Ethics Committee of Shimane University and written informed consent was waived because it was a retrospective analysis of medical records.

We recruited patients who were initially examined using Gd-EOB-DTPA-MRI at Shimane University Hospital from June 2008 to June 2013. All nodules found by that modality were then investigated in detail. Nodules found in patients previously treated for HCC prior to the initial Gd-EOB-DTPA-MRI examination were also excluded. Nodules ≥5 mm in diameter, hypovascular in the arterial phase, and those showing hypointensity in the hepatobiliary phase of Gd-EOB-DTPA-MRI were included, as such nodules were defined as hypovascular nodules for this study.

In addition to histopathologically diagnosis, the HCC diagnosis was also made based on the hypervascularization of the nodules in the arterial phase of Gd-EOB-DTPA-MRI and/or those that showed an enlargement of 2 mm or more in diameter. The nodules were categorized into those that did and did not progress to HCC, and we made comparisons to reveal any factors possibly related to HCC progression. We also analyzed the characteristics of the patients who did and did not have nodules that progressed to HCC.

Clinical variables were compared between the groups using either Mann-Whitney's U test or Pearson's chi-square test. A multivariate analysis was also conducted using the findings of a logistic regression analysis with the factors shown to be significantly different between the groups by Mann-Whitney's U test or Pearson's chi-square test. A p value <0.05 was considered to indicate a statistically significant difference. A Kaplan-Meier time-to-event curve was produced to estimate the cumulative hypervascular transformation of nodules from a hypovascular state. This analysis was also done to estimate the cumulative progression ratio of nodules to HCC. A receiver operating characteristics (ROC) analysis was performed for nodules followed for more than 12 months to determine the cut-off value of the initial nodule size for predicting HCC progression at 12 months.

RESULTS AND DISCUSSION

We identified 91 hypovascular nodules in 28 patients. The mean age of the 28 patients at the time of the initial Gd-EOB-DTPA-MRI examination was 68.8±1.8 (standard error; SE) years old. The mean observation period was 1,172.6±95.6 days. The cumulative ratio of hypervascular transformation was 7.1% at 12 and 12.7% at 24 months. On the other hand, previous reports have shown 14.9% to 43.5% at 12 months. The patients in those previous studies included those with a past HCC treatment history, thus recurrent and intrahepatic metastatic lesions may have been included among the hypervascular transformed lesions investigated. The cumulative ratio of hypovascular nodule progression to HCC was 22.4% at 12 and 29.1% at 24 months.

Among all 91 hypovascular nodules, 33 in 18 patients were finally classified as showing HCC progression. A univariate analysis revealed significant differences in regard to the etiology of liver damage (p=0.001), plasma protein induced by vitamin K absence or antagonist-II (PIVKA-II) concentration (p=0.023), and background liver condition (p=0.039) between the nodule groups. However, according to the multivariate analysis findings, those did not remain as significant predictive factors. While 18 patients had nodules that progressed to HCC, there were 10 patients with nodules that showed no such progression. As for the differences between these patient groups, age (p=0.002) and etiology of liver damage (p=0.013) were found to be significant in a univariate analysis. However, in a multivariate analysis, those did not remain as significant predicting factors. It is difficult to classify hypovascular nodules into those with a high risk of progression to HCC based on background factors alone at the initial time of identification, and thus it is important to closely monitor all hypovascular nodules.

Among 91 hypovascular nodules, 17 were followed for less than 12 months without any progression to HCC. We conducted a ROC analysis of the remaining 74 nodules to predict their progression to HCC at 12 months. The initial nodule size yielded an area under the ROC (AUROC) with a level of 0.745, with an optimal cut-off value of 9.5 mm (sensitivity, 57.9%; specificity, 87.3%). Some previous reports have noted that the initial nodule size is a risk factor for the future development of HCC. Although the present analysis was limited, our results suggested that the initial nodule size of the nodule was useful for predicting HCC progression within 12 months. Takayama et al. reported 9 mm as an optimal nodule size cut-off value for progression to hypervascular and/or an enlarged lesion, very similar to that found in the present study.

CONCLUSION

In patients without any past HCC treatment history, it is difficult to divide hypovascular nodules into those with a high risk of progression to HCC based on background factors alone at the time of initial identification. Since hypovascular nodules have the potential for HCC development, it is important to closely follow up such affected patients.