Response to Reviewer 00722050:

We thank Reviewer 00722050 for contributing to this paper. In this revision, we revised the table to clarify the reference and case presentations.

"There are some minor spellings in the manuscript (e.g., labeling of table 1: case reports)."

We had Nature Research Editing Service of English proofread our English writing and further revised the manuscript as it is shown in red text. Table 1 was revised to simple form.

Response to Reviewer 02733628:

We thank Reviewer 02733628 for contributing to this paper. In this revision, we revised some mistakes we could find and shortened the case presentation and discussions.

"Its medical language, English writings rules and punctuation marks should be corrected and revised. In addition, article should be made shorter, especially case presentation and discussion parts."

We had Nature Research Editing Service of English proofread our English writing and further revised the manuscript as it is shown in red text. Case presentation and discussions are made shorter to be more comprehensive as shown below.

(History of present illness.)

Two cystic lesions, located in the right hepatic lobe with diameters of 6 (anterior tumor: tumor-Ant) and 18 (posterior tumor: tumor-Post) mm, were detected by primary imaging performed in 2004. MRI demonstrated simple liver cysts; ~~Both lesions demonstrated hypointensity on T1- and hyperintensity on T2-weighted magnetic resonance imaging (MRI)~~

~~sequences, which is consistent with simple liver cysts.~~ H~~h~~owever, tumor-Post partially contained abnormal lesions ~~that were hyperintense on T1- and hypointense on T2-weighted sequences~~ (Figure 1).

(Latter half of the TREATMENT.)

Cholangiography during the surgical procedure showed cystic pooling of the contrast media, demonstrating the connection between the bile ducts and cystic tumors (Figure 5) and suggesting that the cystic lesions should be considered IPNB but not mucinous cystic neoplasms. ~~Communication between the cystic tumors and bile ducts in the present case was confirmed by cholangiography during the surgical procedure, and this characteristic communication differentiates IPNB from mucinous cystic neoplasm[4].~~

(Discussion about the surgical procedure in the DISCUSSION.)

hyperenhancement during the arterial phase of CEUS is an effective imaging feature for analyzing IPNB extension.

~~Complete surgical resection is recommended for the treatment of IPNB[18]. Lim et al[20] demonstrated that cystic-type IPNB might be a counterpart of branch-duct IPMN, which is usually a benign tumor. However, they also discuss that surgical resection is necessary because most cases of IPNB are at least carcinoma in situ. Histologically, 61% of IPNBs are invasive[20] and 83% of papillary proliferation complicates adenocarcinoma or mucinous carcinoma[21]. These previous studies support the indication of liver subsegmentectomy in the present case.~~

Response to Reviewer 03647890:

We thank Reviewer 03647890 for contributing to this paper. Although his/her comment requires no revision, we revised the manuscript according to other reviewer's comments.

Response to Reviewer 02954069:

We thank Reviewer 03647890 for contributing to this paper. Although his/her comment requires no revision, we revised the manuscript according to other reviewer's comments.

Response to Reviewer 04870360:

We thank Reviewer 02733628 for his/her important suggestions. In this revision, we revised discussions and introductions as follows.

"1- Authors should mention a previous case report related to its topic like "Intraductal papillary neoplasm of the bile ducts: A case report and literature review. World J Gastroenterol. 2015 Nov 21; 21(43): 12498–12504." and also mention the difference between two cases."

We found that the designated manuscript is reference 11 and revised the comment about the difference as shown below.

(Last part of the DISCUSSION.)

Tan et al[11] reviewed previous studies ~~reported a study~~ of 354 IPNB patients, among whom, 52.8% were from Japan, and 19.5% were from Eeastern countries, including China, Korea and Taiwan, ~~that describes~~which indicates that IPNBs occuring more commonly in the East Asian population than in other populations. There was no previous literature which could detect the tumor progression from the main lesion to other cysts or bile ducts using CEUS.

"2- There are some typos and grammar mistakes so, I encouraged authors to revised the manuscript."

We had Nature Research Editing Service of English proofread our English writing and further revised the manuscript as it is shown in red text.

"3- The introduction section is very short, it required to be informative."

We added comments about previous literatures and diagnostic problems in the introduction as shown below.

(INTRODUCTION)

Intraductal papillary neoplasm of the bile duct (IPNB) is a type of tumor that presents in the common or intrahepatic bile duct and occasionally accompanies mucus production [1]. IPNB shares common characteristics in common with intrapancreatic mucinous neoplasms (IPMNs), which are sometimes malignant [2]. Although the development of IPMNs from pancreatic cysts is well documented because of the high prevalence rate of these neoplasms, there are only a few reports about IPNB development from hepatic cysts. Careful follow-up for the IPNB is recommended because complete and timely surgical resection is required if malignancy is suspected [3]. However, little is known about the natural course of IPNB over a long-term period.

The clinical diagnosis of the IPNB is often made by computed tomography (CT) or magnetic resonance imaging (MRI), however, few studies have reported that contrast-enhanced ultrasonography (CEUS) is useful for diagnosing the tumor. Here, we report a case of IPNB that developed in a normal liver over 13 years with follow-up imaging of hepatic cystic hepatic tumors. We could clearly detect papillary lesions and tumor progressions by CEUS and performed successful resection.

Response to Reviewer 02936110:

We thank Reviewer 02733628 for his/her important suggestions. In this

revision, we provided supplementary figure of the initial tumor biopsy and revised introductions and discussions as follows.

"1. The authors showed that ultrasound-guided histological puncture of tumor-post was performed, and no malignancy was found, and the pathological results should be supplied."

We provided the initial histological figure as a supplementary figure. Comments about the biopsy and further follow-up was revised as shown below.

(Latter part of the History of present illness.)
Because ultrasonography of tumor-Post demonstrated hyperechoic lesions, leading to the suspicion of solid tumors, ultrasound-guided histological puncture of tumor-Post was performed, ~~indicated,~~ and the result showed normal liver tissue with no malignancy (Supplementary Figure 1). Biannual follow-up examinations were performed, ~~Although tumor-Post was suspected to be benign,~~ because there is a possibility that the biopsy missed the target and ~~such as complicated hepatic cysts or inflammatory pseudotumors are,~~ the complex morphology of the cystic tumor had the potential for malignancy.~~, and biannual follow-up was repeated.~~

"2. The characteristic of this case is long term follow up. However, the IPNB has been reported many times. What are the other characteristics of this case? These contents should be fully discussed."

Another characteristic of this case, besides the long-term follow-up, is the usefulness of CEUS as an inspection tool for the follow-up of IPNB as we described in the initial version. To further clearly demonstrate the issue, we changed the conclusion in the abstract and added comments in the introduction and revised the discussion as shown below.

(CONCLUSION of the Abstract)

The development of IPNB should be monitored ~~over decades~~ in patients with cystic ~~hepatic~~ lesions and ultrasonography are useful tool for the evaluation.

(Latter part of the INTRODUCTION)

The clinical diagnosis of the IPNB is often made by computed tomography (CT) or magnetic resonance imaging (MRI), however, few studies have reported that contrast-enhanced ultrasonography (CEUS) is useful for diagnosing the tumor. Here, we report a case of IPNB that developed in a normal liver over 13 years with follow-up imaging of cystic hepatic tumors. We could clearly detect papillary lesions and tumor progressions by CEUS and performed successful resection.

(Last part of the DISCUSSION)

There was no previous literature which could detect the tumor progression from the main lesion to other cysts or bile ducts using CEUS. The present case shows that even if the tumor is followed for over a decade, periodic imaging surveillance is necessary. ~~A detailed examination is needed when the cystic tumor enlarges, or papillary proliferation appears.~~ CEUS is an effective imaging method which can detect the detailed features ~~for the detailed examination~~ of IPNB.

"3. IPNB is classified into four subtypes based on the histomorphology and immune-phenotypical profile: pancreato-biliary, intestinal, gastric, and oncocytic subtypes. The authors should discuss the immunohistochemical results of the case."

Histomorphology and immunohistochemistry findings are important information for the IPNB. We added a comment about their relations in the discussion as shown below.

(DISCUSSION about pathological findings)

The immunohistochemical results of mucin in IPNB are described as follows: MUC2 expression is ~~was~~ common in the intestinal type, and MUC6 is common in the gastric type, and ~~while~~ MUC5AC is ~~was~~ expressed in ~~either~~ both of the phenotypes. As the presented case shows gastric epithelium, the MUC staining results are consistent with the phenotype. ~~Naito et al [7] determined that~~ MUC1 is ~~was~~ positive only in malignant IPNBs, such as pancreato-biliary and oncocytic type neoplasms [7,11]. The lack of mucus secretion corresponds with MUC1 positivity and the malignant potential [19].

"4. Language quality need to be improved."

We had Nature Research Editing Service of English proofread our English writing and further revised the manuscript as it is shown in red text.