

Reply to the reviewers' comments

Question Number	Original comments of the reviewer	Reply by the author(s)	Changes done on page number and line number
Reviewer 1 (05226098): Q1	Please provide the number of patients required to statistically prove this result.	Chi-Chih Wang	We used Stata version 12 for the calculation of number of patients we need in Cox model. When we set power as 0.8 (two tailed), hazard ratio 3.45 comparing subsequent cholangiocarcinoma risk in ES/EPBD group than that in no intervention group, we need 21 cases in each arm. When hazard ratio is 1.31 comparing between ES/EPBD & CCY and no intervention group, we need 431 cases. The power of this study is good.
Reviewer 1 (05226098): Q2	Please describe why the incidence of cholangiocarcinoma is not reduced in the cholecystectomy group within 18 months.	Chi-Chih Wang	The incidence of cholangiocarcinoma is resulted from chronic inflammation in our opinion. Although cholecystectomy can reduce RBEs, the effects of reduction cholangiocarcinoma incidence through lowering RBEs cannot fully been seen in a short observation period. We think this is why the incidence of cholangiocarcinoma is not reduced in the cholecystectomy group within 18 months.
Reviewer 2 (05194798): Q1	(P8L17) Please explain in detail why the authors defined subsequent cholangiocarcinoma as cholangiocarcinoma that occurred after the first 18 months but not after the first 6 months after endoscopic intervention or biliary event.	Chi-Chih Wang	As we can see in Figure 2, the incidence of cholangiocarcinoma is higher not only in the first 6 months but also noticed between 12-18 months after index admission. (5 cases in 6-12 months and another 5 cases in 12-18 months; 11 cases in following 6 years) Because the lack of further detailed image and invasive intervention in the no intervention group at index admission for choledocholithiasis, the possibility of obscured cholangiocarcinoma

			increased. We add some descriptions which marked in red in P9L1-2 in the method section.
Reviewer 2 (05194798): Q2	The authors should describe the definition of the recurrent biliary event.	Chi-Chih Wang	The definition of recurrent biliary events include ER visits or admission course due to cholangitis, cholecystitis or biliary pancreatitis. We clarify this definition on P9L7-10 which marked in red.
Reviewer 2 (05194798): Q3	Is the information regarding number of cholangiocarcinoma after first 6 months necessary?	Chi-Chih Wang	Thanks for the remind, we delete the information about the comparisons of cholangiocarcinoma happened 6 and 12 months after index admission in Table 1. The regarding