

Round 1:

Answering Reviewers:

1. A key point of this strategy is successful cannulation into the gallbladder. Cystic duct direction (proximal/distal, right/left, or cranial/caudal) and length both affects the success of cannulation into the gallbladder. The author should discuss these issues.

Response: Guide wire insertion into the gallbladder is the key to the success of operation. The selective cystic duct intubation strategy should be applied based on the site and direction of the cystic duct incision. Before the operation, operators should read the MRCP image carefully, and know about the site, shape, direction and length of the cystic duct incision. We have found that the gallstones might cause significant dilation of the cystic duct during the process of removing from the cystic duct, and the dilation diameter usually ranged from 0.3cm to 0.8 cm, therefore, the difficulty of the guide wire entering the gallbladder was substantially reduced. Although the location of the cystic duct joining the common bile duct may increase the difficulty, it can be solved by adjusting the entry direction of the guide wire. Among them, entering from the left side is the most difficult, while entering from the right side is relatively easier. For those patients with twisted cystic duct, the difficulty of the guide wire entering into the gallbladder is reduced after dilation by gallstone removing.

2. Factors that predict the successful cannulation into the gallbladder, such as patient characteristics and imaging findings before treatment, should be explained in the Discussion section based on the existing literature.

Response: For those patients without secondary choledocholithiasis, intubation of the cystic duct is not a routine operation of ERCP; for those patients with recently occurred secondary choledocholithiasis, the cystic duct is usually dilated and its incision is widened due to the removing of gallstones, and the cystic duct

intubation becomes easier. Usually the diameter dilated is between 0.3 and 0.8 cm, so the difficulty of entering the guide wire into the gallbladder is reduced substantially. In addition, there is different in operational difficulty depending on the site to enter into the common bile duct through the cystic duct, including the dorsal, ventral, left, and right sides of the common bile duct. But they are all accessible by adjusting the direction of guide wire. Among them, entering from the left side is the most difficult, and entering from the right side is relatively easy. For those patients with twisted cystic duct, the difficulty of entering the guide wire into the gallbladder is reduced after dilation by gallstone removing.

3. The cystic duct dilation process should be described in detail. Was cystic duct dilation not performed if the diameter of the cystic duct was larger than that of the gallstones? How did the author decide on the balloon size for cystic duct balloon dilation? Also, if gallstones are larger than the cystic duct diameter, the cystic duct must be dilated with a balloon that is larger than the cystic duct diameter. If this is the case, is there a high risk for cystic duct injury?

Response: The diameter of cystic duct should be measured with MRCP preoperative, the gallstone can be removed directly without dilating the cystic duct if the diameter of the cystic duct is larger than that of the gallstone; if the diameter of the gallstone is larger than that of the cystic duct, it is necessary to use a balloon to expand the cystic duct to between 1.1 and 1.3 times the diameter of it; this therapy strategy should be abandoned if the gallstone is still larger than the dilated cystic duct. Cystic duct dilation cases only took small portion of the cases we reported (2/6), and cystic duct damage, rupture or necrosis were not occurred due to the elasticity of the cystic duct.

4. The location of gallstones should be shown in detail. Is it possible to remove gallstones anywhere in the gallbladder? Because the inside of the gallbladder is

larger than that of the common bile duct, is it difficult to grasp the stones using a basket or balloon?

Response: We noticed that multiple gallstones are basically similar in size. We select those patients who recently occurred secondary choledocholithiasis, and with countable gallstones to perform transcystic duct exploration. For the convenience of gallstone removing, an appropriate amount of bile should be sucked to narrow the gallbladder before the operation. Either a mesh basket or a balloon can be used for the exploration depending on the location of the gallstone in the gallbladder. When gallstone is located in the body of gallbladder, the mesh basket will be preferred; while if the gallstone is located in the neck of gallbladder or the ampulla of gallbladder, the balloon can be used to push it to the body of gallbladder or pull the gallstone out directly.

5. Diameter, length, and direction of the cystic duct should be shown in Table2.

Response: This is a good suggestion, we thank it very much, and we have listed the diameter, length, and direction of the cystic duct in Table2.

6. The existing Figures2 and 3 (common bile duct stone removal) should be deleted. Instead, Figures2 and 3 should clearly show the process of gallstone removal. Because Figure3 is of poor quality, it is difficult to understand the process of removing gallstones.

Response: Thanks for your suggestion, we have remained and revised Figure2 as this figure shows real-time operation process of gallstones removal; we have replaced Figure3 by higher resolution images and rearranged them into a single PowerPoint file format, and in order to describe the gallstones removal process more clearly, different symbols were used to mark the images in Figure3. We feel so sorry that the definition of the film displayed in Figure3 maybe still poor due to our equipment is aging, although we have tried our best to improve the quality of the

images.

7. Laparoscopic cholecystectomy is the current standard approach for removing gallstones, with few early and late complications. Specific outcomes of established approaches such as laparoscopic cholecystectomy should be described. Furthermore, endoscopic gallstone removal should have complications equal to or greater than those of endoscopic gallbladder drainage.

Response: Laparoscopic cholecystectomy (LC) is a standard surgery therapy for the treatment of benign gallbladder diseases, the common complications for LC include bile duct injury, hemorrhage, biliary fistula, abdominal infection, and duodenal perforation. Besides, chronic diarrhea and malignant tumors of digestive system (colon cancer, pancreatic cancer, esophageal cancer, hepatocellular carcinoma, etc.) may occur due to the loss of gallbladder function after the cholecystectomy. For those patients with secondary choledocholithiasis, ERCP combined with transcystic duct exploration is preferred. The amylase increase in our current patients is a postoperative complication of common bile duct stone removal. One case of cholecystitis was found during the operation of gallstone removal, which was improved after anti-infection and other treatments. We also found that for gallstones larger than 0.8cm in diameter, additional lithotripsy was needed if the cystic duct is not dilated correspondingly, which greatly increased the difficulty and time of the operation, and accordingly increased the occurrence of complications. As a result, we considered 0.8cm as the diameter limit for further reference. In this treatment strategy, patients were free from cholecystectomy, so that gallbladder was preserved and gallbladder function was maintained, which enlarged the benefits to the patients.

Minor comments:

(1) Please show the sequence of magnetic resonance cholangiopancreatography (MRCP) in Figure 1.

Response: Thanks for your suggestion and we have shown the sequence of magnetic resonance cholangiopancreatography (MRCP) in Figure 1.

(2) Figure 1b is of poor quality. Please improve this.

Response: Thanks for your suggestion, we have replaced figure1b with a higher resolution image.

(3) Why did the author establish the cutoff of <0.8 cm diameter gallstone size for patient selection?

Response: According to the pre-clinical observation, more than 95% of patients with secondary choledocholithiasis have the gallstones less than 0.8cm in diameter and it is not smoothly to remove gallstone exceeding this diameter limit. Considering the success rate of gallstone removal, 0.8cm is considered as the cutoff of gallstone size.

(4) Please simplify the description of NOTES in the Discussion section.

Response: Thanks for your suggestion, we have simplified the description of NOTES in the Discussion section.

(5) Although the author established the cutoff of <0.8 cm diameter gallstone size for patient selection, the diameter of gallstones in Patient 1 was 13 mm (1.3 cm). Why did you include this patient in the study?

Response: It was the first patient who had received ERCP combined with transcystic duct exploration treatment in our included cases. During the operation, we successfully removed the gallstones with a mesh basket and then washed the gallbladder. There was no gallstone residual according to the radiography. For the gallstone larger than 0.8cm in diameter, additional lithotripsy was needed if the cystic duct was not dilated correspondingly, which would greatly increase the difficulty and time of the operation, and accordingly the complications. As a result, 0.8cm is considered as the diameter limit of common bile duct for the rest cases.

(6) Please simplify the histories of past illnesses in Table 1.

Response: Thanks for your advice, we have simplified the histories of past illnesses in Table 1.

(7) There are some typographical errors and omissions in your manuscript.

Response: Thanks for your advice and we have modified and polished the English expression of the full text.

Answering editorial office's comments:

(1) I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

Response: we have uploaded the approved grant application form(s) to the submit system.

(2) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Response: We have prepared and arranged the original figures by PowerPoint named "59882-Figures.ppt" in the revised version.

(3) I found the authors did not add the PMID and DOI in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout.

Response: We have revised the format of references and list all authors, as well as added PMID and DOI in the reference list.

(4) The author should number the references in Arabic numerals according to the

citation order in the text. The reference numbers will be superscripted in square brackets at the end of the sentence with the citation content or after the cited author's name, with no spaces.

Response: We have revised the format of citation and deleted spaces according to the editor's requirement.

Round 2:

Thank you for your comments, we have responded and re-revised our manuscript, figures and Tables according to your suggestions.

The details are as follows and have been contained in the uploaded files:

1) In Discussion session, the authors described that "From our current experience, this technology still has certain disadvantages: (1) It is only effective for some patients. It is expected to be successful for those whose with is one or less than 10 calculi, where the diameter of the gallstones is less than 0.8 cm, or in cases where although the diameter of the cystic duct is greater than 0.8 cm, the diameter of the cystic duct is dilated at the same time, and the diameter of calculus is less than 3 mm.". Wasn't the cut-off size of gallstone diameter 8mm?

Response: Thank you for your comments, and we are so sorry for the ambiguous due to the unclear expression. In our study, this technology is not effective for all cases. The duration of operation will be excessively long if there were much more gallstones, thus the count of gallstones less than 10 is recommended, and it is supposed to be smoother if the gallstone's diameter is less than 8mm. As for the gallstones of which the diameter exceeds 8mm, however, if the cystic duct is expanded synchronously, the gallstone with a diameter of 3mm larger than the cystic duct also can be removed. The experience is under improving with the accumulation of cases in our center.

2) Please indicate whether was performed or not in each case in Table2. Should cystic

dilation be performed in cases where the diameter of the cystic duct is equal to that of the diameter of gallstones (patient No. 4 and 5).

Response: Thank you for your suggestion. We have added the information of cystic dilation to the list of Table2. Cystic dilation is not necessary if the diameter of cystic duct is equal to that of gallstone. Therefore, in this report, we removed the gallstones directly without dilating the cystic duct in dealing with Case 4 and 5 whose diameter of cystic duct is proximately to that of gallstone.

3) Although ERCP approach for gallstones is interesting, ERCP is a high-risk procedure, which occasionally can be fatal. Furthermore, some patients may suffer from recurrent cholangitis after endoscopic sphincterotomy. As the author described, laparoscopic cholecystectomy has some disadvantages. However, ERCP have some early and late complications. Although there were no severe complications in your cases, ERCP-related complications (including cystic duct perforation and post-ERCP pancreatitis etc.) should be considered. Please discuss this matter.

Response: Thank you for your suggestion, and we have supplemented ERCP-related complications in the Discussion part of our article. ERCP is one of the preferred therapies for choledocholithiasis. It has been reported that some complications including recurrent cholangitis, pancreatitis, hemorrhage, and perforation occurred after the endoscopic sphincterotomy (EST). There also occurred complications in our preliminary practice 20 years ago. However, the aforementioned complications occurring rate has been reduced significantly after the reported studying curve(180 ~200cases). In our center, ERCP plus EST is safe and effective for the treatment of choledocholithiasis. Arguably, ERCP is quite safe for surgeons with rich experience. However, it is not suitable for inexperienced surgeons (operating less than 200 cases totally, or less than 100 cases annually). Thus, this operation strategy is suggested to be

selectively developed in large and experienced medical center.

4) Please show the sequence of MRCP in Figure 1. Heavy T2 ? B-TFE ?. Furthermore, study time in Figure1 should be deleted. Response: Thank you for your good advice! We have shown the sequence information of MRCP in Figure 1 and deleted study time in Figure 1&Figure2. 5) Please describe why the author included patient No1 who had gallstones of 13mm in the manuscript.

Response: It was the first patient who had received ERCP combined with cystic duct exploration treatment in our included cases. During the operation, we successfully removed the gallstones with a mesh basket and then washed the gallbladder. There was no gallstone residual according to the radiography. For the gallstone larger than 0.8cm in diameter, additional lithotripsy was needed if the cystic duct was not dilated correspondingly, which would greatly increase the difficulty and time of the operation, and accordingly the complications. As a result, 0.8cm is considered as the diameter limit of common bile duct for the rest cases.