Application of endoscopy in the diagnosis of hepatobiliary tumor in patients with hepatolithiasis

Jiaming Xie

Second Affiliated Hospital of Soochow University

Wei Li

Second Affiliated Hospital of Soochow University

Zhenyu Feng

Second Affiliated Hospital of Soochow University

Zhenyu Ye

Second Affiliated Hospital of Soochow University

Jun Pan

Second Affiliated Hospital of Soochow University

Peng Du

Second Affiliated Hospital of Soochow University

Xiaoming Ma

Second Affiliated Hospital of Soochow University

Dekang Gao

Second Affiliated Hospital of Soochow University

Shaohua Wei

Second Affiliated Hospital of Soochow University

Wei Chen (✉ sdfeychenwei1971@126.com)

Second Affiliated Hospital of Soochow University

Technical advance

Keywords: Endoscopy, Hepatobiliary tumor, Diagnosis, Application, Hepatolithiasis

Posted Date: October 23rd, 2019

DOI: <https://doi.org/10.21203/rs.2.16353/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Hepatobiliary tumor is related to hepatolithiasis, early diagnosis and radical resection determines the prognosis. However, to accurately diagnose early hepatobiliary tumor is difficult. Here we evaluated the value of endoscopy in the diagnosis of hepatobiliary tumor in patients with hepatolithiasis.

Methods: Clinical data of 56 patients undergoing choledocholithotomy in the Second Affiliated Hospital of Soochow University from January 2018 to April 2019 were analyzed retrospectively. The mucosa morphology, submucosal vascular density and distortion of the hepatobiliary tracts were observed by choledochoscopy. For the abnormal mucosa, the mucosal properties were further determined from the following aspects: methylene blue or Narrow band imaging (NBI) staining observation of the mucosa, detection of the submucosal structures with the ultra-fine ultrasonic probe under the choledochoscopy, and biopsy of the mucosa. Endoscopic findings of intraoperative hepatobiliary mucosa were verified by biopsy or postoperative pathology results.

Results: Choledochoscopy or ultra-fine choledochoscopy was performed on 56 patients with hepatolithiasis, hepatobiliary mucosa was observed then. Among the 56 patients, we found five patients with hepatolithiasis complicated with hepatobiliary tumor, either benign or malignant (8.93%): one case of early cholangiocarcinoma; one case of invasive cholangiocarcinoma; Three cases of hepatobiliary adenomas. one was cholesterol polyp of the gallbladder with local adenomatous hyperplasia of the glands, one was multiple adenomas of the intrahepatic and extrahepatic bile ducts with low-grade intraepithelial neoplasia, and another one was adenomatous hyperplasia of the intrahepatic ducts. Corresponding cholangioscopic images and postoperative pathology results were obtained in all cases.

Conclusions: Intraoperative cholangioscopic exploration can accidentally find tumors of the hepatobiliary system besides calculi. Endoscopic staining and observation of the hepatobiliary mucosa under direct vision has important clinical significance and value in the screening of diseases associated with calculi of the hepatobiliary system like hepatobiliary tumors, especially the early cancer of the hepatobiliary tracts.

Introduction

Diseases of the hepatobiliary system are common in China. Stones, infections, tumors, parasitic diseases and choledochal cysts can all occur and they often interact with each other as both cause and effect. For example, infections can promote the formation of gallstones, which can cause acute or chronic inflammation, and the chronic inflammatory stimulation of gallstones may be related to the occurrence of cancer^[1-2]. Hepatobiliary carcinoma is a malignant tumor with poor prognosis in the digestive system and is reported a close relationship with hepatolithiasis in the literature^[3-6]. Based on high malignancy, poor prognosis and lower survival rate^[7-8], early diagnosis and radical resection are crucial for patients^[9-10].

At present, preoperative diagnosis of hepatobiliary carcinoma mainly depends on physician experience and imaging examination ^[11–14]. However, for the early cancer of the hepatobiliary system, the detection rate is rare. Therefore, how to improve the accurate diagnosis of early hepatobiliary carcinoma is a difficult problem in clinical practice. Diagnosis and treatments of early gastrointestinal cancer through endoscopy made remarkable achievement for a decade ^[16–18], as the same cavity organs of digestive tract like hepatobiliary system, the experiences of endoscopic diagnosis and treatment of early gastrointestinal cancer can be used for diseases of hepatobiliary system. However, the anatomy of hepatobiliary system is complex than the gastrointestinal, for the intrahepatic bile duct branches step by step, conventional choledochoscopy cannot detect all the intrahepatic bile ducts, blind areas are existing which make the application of endoscopy restricted. With the application of ultrafine cholangioscopy ^[19–20], which overcome the blind areas, endoscopic diagnosis and treatment for early hepatobiliary carcinoma is feasible and is worth exploring.

In this study, we innovatively applied ultra-fine soft mirror to achieve complete direct vision of the hepatobiliary tracts, eliminate the blind areas and performed routine intraoperative choledochoscopy on 56 patients with hepatolithiasis, aiming to explore the application value of endoscopy in the diagnosis of hepatobiliary tumors, especially early cancer of the hepatobiliary system.

Materials And Methods

General information

Retrospective analysis was conducted to collect the clinical data of 56 patients with hepatolithiasis in the department of hepatobiliary surgery of the Second Affiliated Hospital of Soochow University from January 2018 to April 2019. Among the 56 patients aged from 20 years old to 89 years old, with an average age of 58.95 ± 2.07 years old, 27 were males and 29 were females. All the 56 patients with hepatolithiasis involved in this study were approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University. Patients and their families agreed the examination through ultra-fine choledochoscopy, ultrasonography, staining of biliary mucosa and biopsy. Informed consent form was signed before the surgery.

Methods and observation indexes

Patients with hepatolithiasis were examined by choledochoscopy during the operation and corresponding images were obtained. According to the images, we first determined whether the mucosa was normal or abnormal by observing the mucosal morphology, submucosal vascular density and distortion of the hepatobiliary tracts ^[21–22]. If the mucosa is normal, the further inspection will be terminated; otherwise if abnormal mucosa is suspected, the mucosal properties will be further determined from the following aspects: methylene blue or NBI staining observation of the mucosa, detection of the submucosal structure level with the endobronchial ultrasonography (EBUS) under the choledochoscope ^[23–24] and

intraoperative biopsy of the mucosa. The endoscopic findings of hepatobiliary mucosa were further verified by pathology results.

Main outcome measures: (1) preoperative imageological diagnosis. (2) intraoperative choledochoscopic results mainly included mucosal deformation, submucosal vascular density and distortion, morphology of the proliferative lesions and changes in the mucosal vessels around the lesions. (3) biopsy or postoperative pathology results.

Statistical analysis

SPSS21.0 statistical software was used for analysis. Mean $\pm$ SE was used to represent the measurement data of normal distribution; absolute logarithm or percentage was used to represent the counting data. $p < 0.05$ was considered statistically significant.

Results

Choledochoscopy or EBUS were performed on 56 patients with hepatolithiasis, hepatobiliary mucosa was observed then. Mucosa staining, ultrasound or biopsy was performed under suspicious circumstances. Among the 56 patients, we found five patients with hepatolithiasis complicated with hepatobiliary tumor, either benign or malignant (8.93%), which are reported as follows:

Diagnosis of malignant hepatobiliary tumor

Among the five patients, we found two malignant hepatobiliary tumor cases, one was early cholangiocarcinoma(Fig.1) and the other one was invasive carcinoma(Fig.2), both of them were confirmed by the postoperative pathology results.

The patient with early cholangiocarcinoma was diagnosed of intrahepatic and extrahepatic bile duct stones by preoperative MRCP (Fig.1A-C). Intraoperative endoscopic exploration and electron staining under choledochoscopy revealed abnormal mucosa at the opening of the original cystic duct in the common bile duct. Compared to normal mucosa (Fig.1D and F), the disorder and rigidness of the veins could be clearly seen after NBI staining (Fig.1E and G). Intraoperative rapid pathology showed focal epithelial high-grade intraepithelial neoplasia (Fig.1 H) and postoperative immunopathology confirmed epithelial high-grade intraepithelial neoplasia of gallbladder neck with focal carcinoma infiltrating muscle wall (Fig.1 I).

The patient with invasive carcinoma was diagnosed of common bile duct stones with soft tissue mass and dilated bile ducts by preoperative CT (Fig.2 A and B). Endoscopic retrograde cholangiopancreatography (ERCP) was failed because the stone could not be removed at all. Laparoscopic choledocholithotomy (LC) was taken then and intraoperative endoscopy found a stone-like mass at the lower part of the common bile duct. After trying to grasp the stone with stone basket catheter for several times, we finally found a blood vessel at the root of the mass when endoscopy came closely to the stone-like mass. NBI staining further confirmed the exist of the blood vessels which means the

stone-like mass was not a true stone, it may be a tumor (Fig.2 C-E). The LC was then converted to open pancreaticoduodenectomy, surgical specimen was seen in Fig.2 F and postoperative immunopathology showed carcinosarcoma of the common bile duct (Fig.2 G-I).

Diagnosis of benign hepatobiliary tumor

Among the five patients, we found three benign hepatobiliary tumor cases, one was cholesterol polyp of the gallbladder with local adenomatous hyperplasia of the glands (Fig.3), one was multiple adenomas of the intrahepatic and extrahepatic bile duct with low-grade intraepithelial neoplasia (Fig.4) and another one was adenomatous hyperplasia of the intrahepatic bile duct (Fig.5).

The patient with gallbladder polyp was admitted to hospital for laparoscopic gallbladder remaning cholecystolithotomy. During the surgery, intraoperative choledochoscopy found an adenoma besides the polyp (Fig.3 A and B) and laparoscopic cholecystectomy (LC) was then taken instead. Postoperative pathology results showed hemi-cholesterol polyp with adenomatuous hyperplasis (Fig.3 C).

The patient with multiple adenomas of the intrahepatic and extrahepatic bile duct was diagnosed of choledocholithiasis with hepatobiliary duct dilatation by CT and MRCP (Fig.4 A-C). Laparoscopic choledochoscopy was performed and besides stones, we found multiple segmental floccules in the hepatobiliary tracts. NBI staining showed tortuous vessels under the floccules, however, the mucous membrane was smooth (Fig.4 D-G). Biopsy pathological results showed adenoma with low grade intraepithelial neoplasia (Fig.4 H and I).

Another adenomatous hyperplasia patient was diagnosed of gallstones, cholecystitis and hepatolithiasis by MRCP (Fig.5 A-C). Laparoscopic choledochoscopy performed and the large stones in intrahepatic bile duct were broke to pieces by green laser and was grasped through stone basket catheter, after we broke one of the stones, a proliferative lesion was seen stick to the bile duct wall (Fig.5 D). The lesion was soft, the mucous membrane was smooth and the tortuous vessels below are clearly visible through NBI or methylene blue staining (Fig.5 E and F).

Discussion

Hepatolithiasis especially intrahepatic cholelithiasis is relatively rare in western countries, with the prevalence of only 0.6% to 1.3%. In some countries in east and southeast Asia, intrahepatic bile duct calculi are a common disease with a prevalence rate of 2%–25% [6], and it is highly correlated with the incidence of hepatobiliary cancer [25–26]. It has been reported in the literature that 70% of the patients with hepatobiliary carcinoma who received hepatectomy in Taiwan were complicated with hepatolithiasis, while 6%–18% of the patients with hepatobiliary carcinoma in Japan were complicated with hepatolithiasis [27]. Among the global patients with intrahepatic bile duct stones suffering from cholangiocarcinoma, China accounts for 3.6% to 10.0% [6].

Hepatobiliary carcinoma accounted for 3% of digestive tract tumors [28]. Due to its atypical clinical manifestations, early diagnosis was difficult, and most of the cases were found in the advanced stage and lost the opportunity of surgery [5,29]. Therefore, the early diagnosis of hepatobiliary carcinoma is particularly important, but how to improve the accurate diagnosis of early cancer of the hepatobiliary system is a difficult clinical problem. Following the successful application experience of endoscopy in the diagnosis and treatment of early gastrointestinal cancers, the endoscopy application of diseases in the biliary tract is also worthy exploring and discussion. Besides, the ultrafine choledochoscopy enables to enter the bile ducts of all branches of the liver without obstacles which laid a foundation for the diagnosis of the hepatobiliary tumors, especially those in the bile ducts with small branches.

Based on the high incidence of hepatolithiasis in China, the close relationship between the hepatic cholangiocarcinoma and hepatolithiasis, the experience of endoscopy application in diagnosis and treatment of early gastrointestinal cancer and the detectable blind area of biliary system through superfine choledochoscopy, the improvement of accurate diagnosis and treatment of early hepatic cholangiocarcinoma by observing the mucous through choledochoscopy, NBI or meilan staining and endoscopic ultrasound, is predictable and beneficial to the patients. As for the two cases of hepatobiliary cancer patients accidentally discovered by our team through choledochoscopy during surgery, timely detection, active diagnosis and treatment will undoubtedly improve the surgical efficacy and prognosis of the patients. In addition, we also found that during the operation of the lower bile duct carcinoma, the cutting edge can be determined by endoscopic observation of the bile duct mucosa, which can avoid repeated resection due to positive pathological detection of the cut edge and then shorten the operation time.

In the diagnosis and treatment of other diseases of the hepatobiliary system with stones, such as benign tumors of the hepatobiliary system, combined application of choledochoscopy and ultra-fine choledoscopy can be used to determine the mucosa around the suspicious lesion, the exist and depth of infiltration. Biopsy can be used to confirm the nature of the lesion. For the endoscopic resection of benign diseases such as polyps or adenomas, it is necessary to learn the operation technologies or skills from the endoscopic diagnosis and treatment of early gastrointestinal cancer. Meanwhile, developing related instruments suitable for the operation of tumor resection, electrocoagulation and hemostasis under ultra-fine choledochoscopy is well worth further discussion and laser electrocution may be feasible then. At this point, we are trying endoscopic mucosal resection (EMR) for tumors of the hepatobiliary system.

In conclusion, endoscopy has a high clinical application value in the auxiliary diagnosis of hepatobiliary tract diseases, which can improve the diagnostic accuracy, avoid misdiagnosis and reduce missed diagnosis. However, a large number of clinical data are still needed to further verify the value of endoscopy in the diagnosis of hepatobiliary tract diseases. In addition, endoscopy is still in the exploratory stage in the endoscopic treatment of biliary tumors, especially early cancer or benign diseases of the hepatobiliary system. The research and development of endoscopic treatment methods or technologies for hepatobiliary diseases, the related instruments under endoscopic treatment are worth further discussion and verification.

Abbreviations

NBI: Narrow Band Imaging; EBUS: Endorochial Utrasoundography; CT: computerized tomography; MRCP: Magnetic Resonance Cholangiopancreatography; ERCP: Endoscopic Retrograde Cholangiopancreatography; LC: Laparoscopic choledocholithotomy; EMR: Endoscopic Mucosal Resection.

Declarations

- Ethics approval and consent to participate

All the 56 patients with hepatolithiasis involved in this study were approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University. Patients and their families agreed the examination through ultra-fine choledochoscopy, ultrasonography, staining of biliary mucosa and biopsy during the surgery. Informed consent form was signed before the surgery and can be achieved from the medical record room of the hospital.

- Consent to publish

Not Applicable

- Availability of data and materials

The clinical datasets of the participants used and/or analyzed during the current study available from the medical record room of the hospital. The datasets of the imagological examination and pathology results used and/or analyzed during the current study available from the Neusoft PACS system of the hospital. The datasets of the choledochoscopic videos available from the corresponding author on reasonable request.

- Competing interests

The authors declare that they have no competing interests.

- Funding

This study was supported by found of Suzhou Introduced Team of Clinical Medical Experts (SZYJTD201803); National Natural Science Foundation of China (81602613); Medical and Health Technology Projects of Suzhou New District (2018Z013)

- Authors' Contributions

J. M. X. and W. C. wrote the paper; W. L., Z. Y. Y., J. P., P. D., X. M. M., S. H. W., and W. C. performed the endoscopic operations; J. M. X., Z. Y. F., D. K. G. collected and analyzed the patients' data. J. M. X., W. L. and W. C. provided funding acquisition.

Not Applicable

References

1. Vetrone G, Emolani G, Grazi GL, et al. Surgical therapy for hepatolithiasis: a Western experience[J]. J Am Coll Surg, 2006,202(2):306-312.
2. Xia Lei, Ma Yougang, Wu Mengchao. Clinical significance of serum CA19-9 in biliary tract diseases [J]. Chin J Hepatobiliary Surg, 2008, 14(3):170-172.
3. Razumilava N, Gores GJ. Cholangiocarcinoma[J]. Lancet,2014,383(9935):2168-79.
4. Rizvi S, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. Gastroenterology [J]. 2013,145:1215– 1229.
5. Kim HJ, Kim JS, Joo MK, et al. Hepatolithiasis and intrahepatic cholangiocarcinoma: A review. World J Gastroenterol, 2015,21(48):13418-13431.
6. Yuan Bo, Miao Jingqi, Chen Yu. Clinical analysis of partial hepatectomy of intrahepatic bile duct calculi[J]. International Medicine and Health Guidance N, 2011,17(10):1176.
7. Kond S, Hirano S, Ambo Y, et al. Forty consecutive resections of hilar cholangiocarcinoma with no postoperative mortality and no positive ductal margins: results of a prospective study[J]. Ann Surg, 2004,240(1):95.
8. Maithel SK, Gamblin TC, Kamel I, et al. Multidisciplinary approaches to intrahepatic cholangiocarcinoma[J]. Cancer, 2013, 119(22): 3929-3942.
9. Esnaola NF, Meyer JE, Kamchristos A, et al. Evaluation and management of intrahepatic and extrahepatic cholangiocarcinoma[J]. Cancer, 2016,122(9):1349-1369.
10. Neuhauser P, Jonas S, Bechstein WO, et al. Extended resections for hilar cholangiocarcinoma[J]. Ann Surg, 1999,230(6):808.
11. Garber SJ, Donald JJ, Lees WR. Cholangiocarcinoma: ultrasound features and correlation of tumor position with survival[J]. Abdom Imaging, 1993,18(1):66-69.
12. Tillich M, Mischinger HJ, Preisegger KH, et al. Multiphasic helical CT in diagnosis and staging of hilar cholangiocarcinoma[J]. Ann J Roentgenol, 1998,171(3):651-658.
13. Hanninen EL, Pech M, Jonas S, et al. Magnetic resonance imaging including magnetic resonance cholangiopancreatography for tumor localization and therapy planning in malignant hilar obstructions[J]. Acta Radiol, 2005,46(5):462-70.
14. Wang Xiaoyu, Shang Hua, Zhou Huiqing, et al. MRI application in diagnosis of extrahepatic cholangiocarcinoma[J]. International Journal of Medical Radiology, 2019,42(4):447-449.

15. Makazu M, Hirasawa K, Sato C, et al. Histological verification of the usefulness of magnifying endoscopy with narrow band imaging for horizontal margin diagnosis of differentiated type early gastric cancers[J]. *Gastric Cancer*,2018,21(2):258-266.
16. Zhang Ying, Shen Lei. The diagnostic value of blue laser magnification endoscopy VS classification for gastric precancerous lesions and early cancers [J]. *Chinese Journal of Digestive Endoscopy* 2018,35(6):385.
17. Tsujii Y, Kato M, Inoue T, et al. Integrated diagnostic strategy for the invasion depth of early gastric cancer by conventional endoscopy and EUS[J]. *Gastrointest Endosc*,2015,82(3):452-459.
18. Choi J, Kim SG, et al. Endoscopic prediction of tumor invasion depth in early gastric cancer[J]. *Gastrointest Endosc*,2011,73(5):917-927.
19. Jin Hao, Liu Huichun, Li Zongkuang et al. Application of ultrafine choledochoscopy in percutaneous transhepatic bile duct tumor biopsy [J]. *Chinese Journal of General Surgery*, 2017,17(8):698-700.
20. Yu Tao, Guo Lei. Superfine choledochoscope combined with cholecystectomy for choledocholithiasis [J]. *Modern Diagnosis & Treatment*,2015, (22):5066-5067.
21. Muto M, Nakane M, Katada C, et al. Squamous cell carcinoma in situ at oropharyngeal and hypopharyngeal mucosal sites [J]. *Cancer*, 2004,101(6):1375-1381.
22. Li Shu, Yu Dongliang, Wang Xin, et al. Clinical study of early esophageal carcinoma by non-magnifying narrowband light imaging endoscopy based on mucosal vascular branches[J]. *Chinese Journal of Digestive Endoscopy*,2019,36(4):273-276.
23. Hurter T, Hanrath P. Endobronchial sonography in the diagnosis of pulmonary and mediastinal tumors[J]. *Dtsch Med Wochenschr*,1990,115(50):1899-1905.
24. Wu Yuwei, Peng Guiyong, Hu Wenhua, et al. The value of endoscopic ultrasound probe in diagnosis and treatment of upper gastrointestinal submucosal tumors[J]. *practical journal of medicine & pharmacy*,2010,27(11):978-979.
25. Shin HR, Oh JK, Masuyer E, et al. Epidemiology of cholangiocarcinoma:an update focusing on risk factors[J]. *CancerSci*,2010,101(3):579-85.
26. Patel T. Cholangiocarcinoma[J]. *Nat Clin Pract Gastroenterol Hepatol*. 2006 Jan;3(1):33-42.
27. Okuda K, Nakanuma Y, Miyazaki M. Cholangiocarcinoma: recent progress Part 1: epidemiology and etiology[J]. *J Gastroenterol Hepatol*,2002,17:1059-1055.
28. Khan S A, Thomas H C, et al. Cholangiocarcinoma[J]. *Lancet*,2005,366:1303-1314.
29. Singhal D, van-Gulik TM, Gouma DJ, et al. Palliative management of hilar cholangiocarcinoma[J]. *Surg Oncol*, 2005,14(2):59-74.

Figures

Figure 1

Endoscopic diagnosis of early hepatobiliary cancer

Figure 2

Endoscopic diagnosis of carcinoma of the lower common bile duct

Figure 3

Gallbladder polyp with local adenomatous hyperplasia

Figure 4

Multiple segmental adenomas in the hepatobiliary tracts

Figure 5

Intrahepatic bile duct stones with proliferative lesions of bile duct