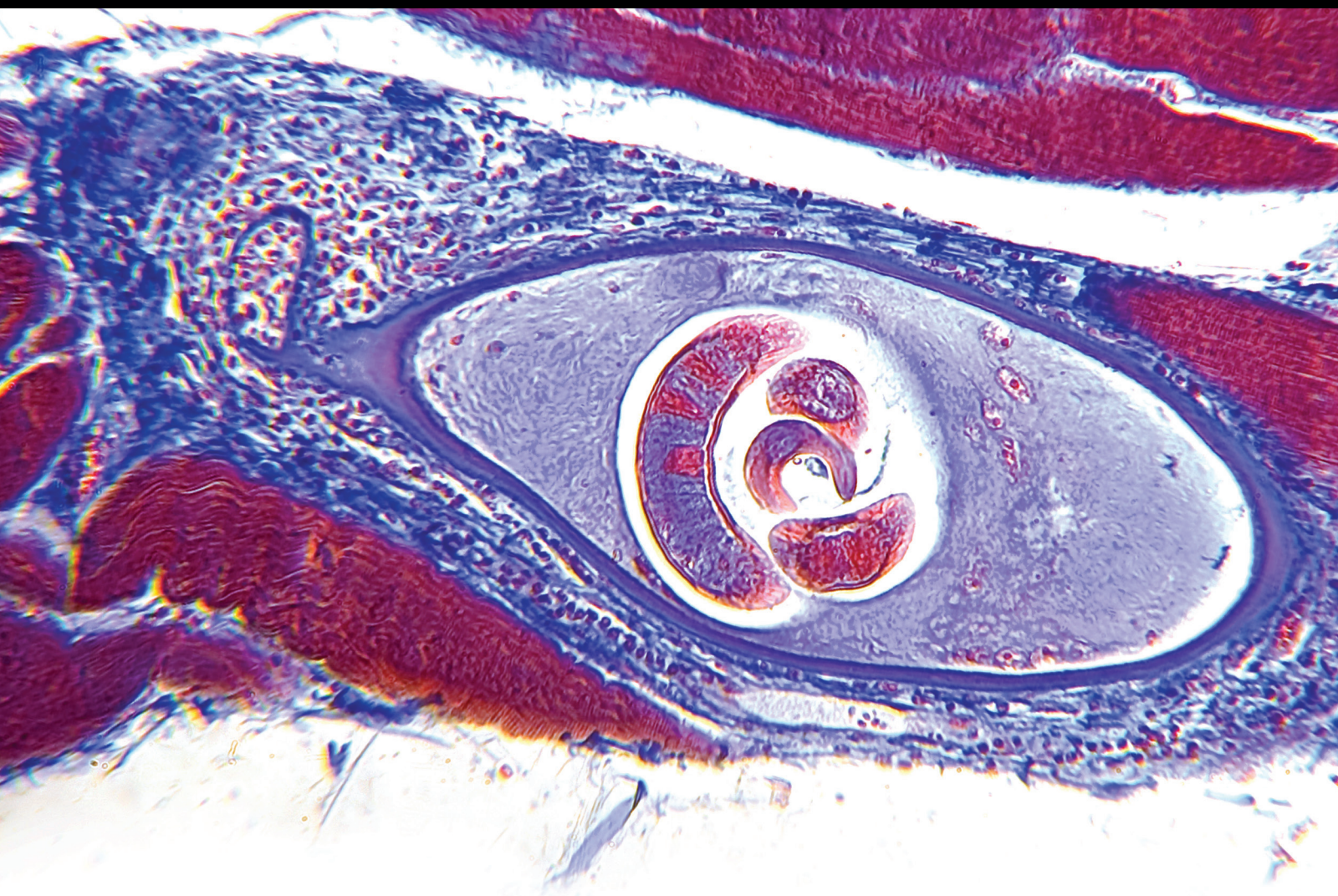
Gastroenterology Research and Practice

Advances in Biliary Tract Disorders: Novel Biomarkers, Pharmacotherapies, Endoscopic Techniques, and Surgical Management

Guest Editors: Mohamad H. Imam, Sooraj Tejaswi, Mohammed Nabil Quraishi, and James H. Tabibian



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Hindawi Publishing Corporation
Gastroenterology Research and Practice
Volume 2016, Article ID 1583486, 2 pages
http://dx.doi.org/10.1155/2016/1583486

Editorial

Advances in Biliary Tract Disorders: Novel Biomarkers, Pharmacotherapies, Endoscopic Techniques, and Surgical Management

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Received 9 November 2016; Accepted 9 November 2016

Biliary tract disorders encompass a wide range of benign and malignant disease processes. In this special issue, we aimed to highlight advances in novel biomarkers, pharmacotherapies, endoscopic techniques, and surgical management of a variety of biliary tract disorders. Such advances continue to lead to improved diagnostic accuracy, better therapies, and subsequently superior patient outcomes. Manuscripts selected for publication in this issue come from around the world and address clinically relevant topics and advances in biliary tract disorders, as briefly summarized below.

Endoscopic retrograde cholangiopancreatography (ERCP) is an established procedure with numerous applications in biliary tract disorders. However, it may be associated with several periprocedural complications, including acute pancreatitis and cholangitis. The presence of periampullary diverticula (PAD) may influence the technical success and safety of ERCP and hence affect patient outcomes. Z. Sun et al. evaluate the difference in clinical outcomes between 161 patients with PAD as compared to matched controls.

Technical modifications and ancillary techniques to ERCP are areas of ongoing research. A strategy that involves placement of a biliary stent to avoid sphincterotomy in patients undergoing ERCP for common bile duct stones is described by T. Ueda et al.; preserving papillary integrity via such a technique may be especially desirable in younger patients. The use of endoscopic ultrasound (EUS) guided biliary drainage as an alternative treatment for biliary obstruction in cases of failed ERCP is growingly implemented; J. Guo et al. describe the outcomes of their experience utilizing this approach for the management of biliary obstruction. T. A. P. Franzini et al. provide an overview of various cholangioscopy techniques and comment on recent advances in visualization of the biliary system and its application to biliary disease management.

Evolution of specific surgical techniques such as those employed in Roux-en-Y hepaticojejunostomy is reviewed from a technical standpoint by D. Moris et al. They summarize their 25-year experience with RYHJ for management of bile duct injury and different perioperative measures they implement to optimize patient outcomes.

Various malignancies have been associated with primary biliary diseases. Optimization of surveillance strategies and care for these patients is crucial. A review manuscript by V. Hrad et al. summarizes the cancer risks found in different primary biliary diseases, including primary sclerosing cholangitis, primary biliary cholangitis, and overlap syndrome. This is complemented by a review paper in which L. Z. C. T. Pu et al. discuss evidence for best practice in management of malignant biliary strictures. For unresectable intrahepatic cholangiocarcinoma, treatment options are limited and often disappointing.

R. Seidensticker et al. aim to assess the outcomes of patients with unresectable intrahepatic cholangiocarcinoma treated by a tailored therapeutic approach, combining systemic and advanced image-guided local or locoregional therapies.

Lastly, gallstone disease remains a major public health burden worldwide. A. Hayasaki et al. aim to identify significant independent variables influencing postoperative hospital stay and medical costs in patients with definite, suspected, or unmatched acute cholecystitis diagnosis according to the 2013 Tokyo Guidelines.

We hope the manuscripts in this special issue will highlight useful advances in the field and help lay groundwork for further studies addressing the etiopathogenesis, diagnosis, and management of biliary tract disorders.

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Hindawi Publishing Corporation
Gastroenterology Research and Practice
Volume 2016, Article ID 9469472, 6 pages
http://dx.doi.org/10.1155/2016/9469472

Clinical Study

Endoscopic Ultrasound-Guided Biliary Drainage Using a Fully Covered Metallic Stent after Failed Endoscopic Retrograde Cholangiopancreatography

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Received 21 January 2016; Accepted 28 June 2016

Academic Editor: Sooraj Tejaswi

Background and Study Aims. Endoscopic ultrasound- (EUS-) guided biliary drainage (EUS-BD) is an alternative treatment for biliary obstruction after failed endoscopic retrograde cholangiopancreatography (ERCP). In this study, we present the outcomes of inpatients with obstructive jaundice treated with EUS-BD using a fully covered metallic stent after failed ERCP. *Patients and Methods.* A total of 21 patients with biliary obstruction due to malignant tumors and prior unsuccessful ERCP underwent EUS via an intra- or extrahepatic approach with fully covered metallic stent between March 2014 and October 2015. A single endoscopist performed all procedures. *Results.* Seven patients underwent hepatogastrostomy (HGS) and 14 underwent choledochoduodenostomy (CDS). The technical and clinical success rates were both 100%. There was no difference in efficacy between HGS and CDS. Adverse events occurred in three patients, including two in the HGS group (1 bile leakage and 1 sepsis) and one in the CDS group (sepsis). Four patients died as a result of their primary tumors during a median follow-up period of 13 months (range: 3–21 months). No patient presented with stent migration. *Conclusion.* EUS-BD using a fully covered metallic stent appears to be a safe and effective method for the treatment of obstructive jaundice.

1. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) has become the first-line therapy for bile duct drainage [1, 2]. In the hands of experienced endoscopists, conventional ERCP results in a failed-cannulation rate of only 3%–5%. Most failures are associated with altered anatomy (e.g., because of previous surgery such as surgical bypass, gastrectomy or Whipple resection) or technical difficulties related to duodenal or biliary obstruction [3]. Percutaneous or surgical interventions are mandatory in patients with failed ERCP but are associated with considerable morbidity and mortality [4, 5]. Interventional EUS is a minimally invasive procedure, and EUS-BD has recently been developed as a salvage therapy for transpapillary treatment [6–9]. The first case reports of EUS-guided transgastric (hepatogastrostomy, HGS) and transduodenal (choledochoduodenostomy, CDS) biliary drainage using plastic or metallic stents were published in the early 2000s [10, 11], followed by subsequent case series [12–16].

The current study aimed to report the outcomes of EUS-BD using a fully covered metallic stent for the treatment of 21 patients with obstructive jaundice and failed ERCP.

2. Patients and Methods

2.1. Patients. All patients who presented with obstructive jaundice and underwent EUS-BD with placement of a fully covered metallic stent after failed ERCP were entered into the study. A total of 45 patients suffered from obstructive jaundice and underwent failed ERCP in our endoscopy center from March 2014 to October 2015. Sixteen of these patients underwent percutaneous transhepatic biliary drainage (PTBD) and eight underwent surgery. The remaining 21 patients underwent EUS-BD and were included in the current study.

This study was approved by the Institutional Review Board and Ethics Committee of China Medical University. All patients chose their therapeutic course voluntarily and provided written informed consent for their participation in

this study. All drainage procedures were performed by the same endoscopist who was familiar with interventional EUS techniques.

2.2. Procedures. The equipment used included a linear array echoendoscope (EG3830UT; Pentax, Tokyo, Japan) with an adjustable ultrasonic frequency of 5, 7.5, or 10 MHz, in combination with an ultrasound scanner (EUB 6500; Hitachi, Tokyo, Japan). 19-gauge needle (EUS N-19-T; Wilson-Cook Medical, Winston-Salem, NC, USA) was used for puncture. A 0.035-inch guidewire (Jagwire; Boston-Scientific, Natick, MA, USA) was used for guidance. A cystotome (10 Fr; Wilson-Cook Medical) was used to dilate the tract and create a large fistula. A fully covered metallic stent (Wilson-Cook Medical, Winston-Salem, NC, USA) was used for biliary drainage. Prophylactic intravenous antibiotics (ceftriaxone, 1 g) were administered routinely twice daily for at least 2 days after the procedure.

2.3. EUS-Guided HGS (EUS-HGS) (Figure 1). EUS-HGS was usually performed in patients who suffered from proximal bile duct obstruction, surgically altered anatomy, or duodenal-bulb invasion.

The intrahepatic approach was performed via the neighboring gastrointestinal tract to allow visualization of the left intrahepatic bile ducts. The usual puncture point was in the cardia or the lesser curvature of the stomach. The echoendoscope was advanced into the stomach. After checking the local vasculature by color Doppler, the 19 G EUS puncture needle was then advanced into the intrahepatic duct and cholangiography was performed, which usually delineated the dilated biliary tree down to the point of obstruction. A guidewire was then inserted through the needle and a cystotome was used to create a fistula between the stomach (or jejunum in patients with total gastrectomy) and the left hepatic duct. Once the fistula had been dilated, a fully covered self-expandable metal stent (SEMS) (8–10 diameter × 4–10 cm long, fully covered with a silicon membrane) was inserted and deployed transmurally. To avoid bile leakage into the peritoneum, a 7 Fr nasobiliary catheter was sometimes placed through the metallic stent for 48 h. Sometimes an uncovered SEMS was placed through the covered stent to avoid stent migration.

2.4. EUS-Guided CDS (EUS-CDS) (Figure 2). EUS-CDS was usually performed in patients who suffered from mid or distal bile duct obstruction or insufficient intrahepatic bile duct dilatation.

For CDS, the needle was directed towards the hilar (proximal) bile duct by maintaining a long scope position, usually from the duodenal bulb. This was important because an upward needle orientation facilitated the procedure by decreasing the angle for transmural stent advancement into the bile duct. After placement of a guidewire, a fistula was created using a cystotome, to pass the stent into the bile duct. Once the fistula was dilated, an SEMS (fully covered) was inserted and deployed transmurally.

3. Results

A total of 21 patients (15 male, 6 female; mean age 67 years, range 41–79 years) were included in the study. The biliary obstruction was malignant in all cases. The reasons for failed ERCP were duodenum stenosis ($n = 9$), surgical bypass ($n = 1$), biliary cannulation failure associated with periampullary tumor infiltration ($n = 10$), and altered position of the ampulla ($n = 1$). The causes of duodenal stenosis were pancreatic carcinoma ($n = 4$), ampullary carcinoma ($n = 3$), and duodenal carcinoma ($n = 2$). Surgical bypass was associated with a previous gastrectomy.

Seven patients underwent HGS and 14 underwent CDS. Both the technical and the clinical success rates were 100%. Bilirubin levels fell in all patients after the procedure. There was no difference in efficacy between HGS and CDS. Adverse events occurred in three patients, including two in the HGS group (1 bile leakage and 1 sepsis) and one in the CDS group (sepsis). A 7 Fr nasobiliary catheter was placed through the metallic stent in the two patients who suffered sepsis, after which the body temperature of both patients returned to normal within 48 h. An uncovered SEMS was placed through the covered stent in one case to avoid stent migration.

Patients were followed up for a mean of 13 months (range: 3–21 months). During this period, four patients died as a result of their primary tumors, two patients presented with stent occlusion, and successful recanalization was achieved in both patients. No patient presented with stent migration.

4. Discussion

Technologic advances in echoendoscopes, processors, and accessories have allowed EUS to progress from a largely diagnostic to a therapeutic modality [17]. The widespread adoption of minimally invasive surgery and radiologic procedures has led to an increase in the use of therapeutic EUS for the curative and/or palliative treatment of gastrointestinal and pancreaticobiliary diseases [17].

Endoscopic retrograde cholangiography with BD remains the most frequent method for palliation of malignant biliary obstruction, with cases of ERCP failure traditionally being referred for either PTBD or surgery. However, both PTBD and surgery have relatively high complication rates, which, together with patient dissatisfaction associated with external drainage, make these options undesirable. Khashab et al. [18] compared the efficacy, safety, and cost of EUS-BD and PTBD in jaundiced patients with distal malignant biliary obstruction after failed ERCP. A total of 73 patients with failed ERCP subsequently underwent either EUS-BD ($n = 22$) or PTBD ($n = 51$), and although the clinical success rates were equivalent (92.2% versus 86.4%, $P = 0.40$), EUS-BD was associated with fewer adverse events (18.2% versus 39.2%) and lower total costs.

EUS-BD has emerged as an effective alternative over the last decade, with significant potential as a minimally invasive and low-risk method of biliary access. Since 2008, numerous studies on EUS-BD have reported high technical and functional success rates and adverse event rates of 3%–23% [6, 7, 9, 19–27].

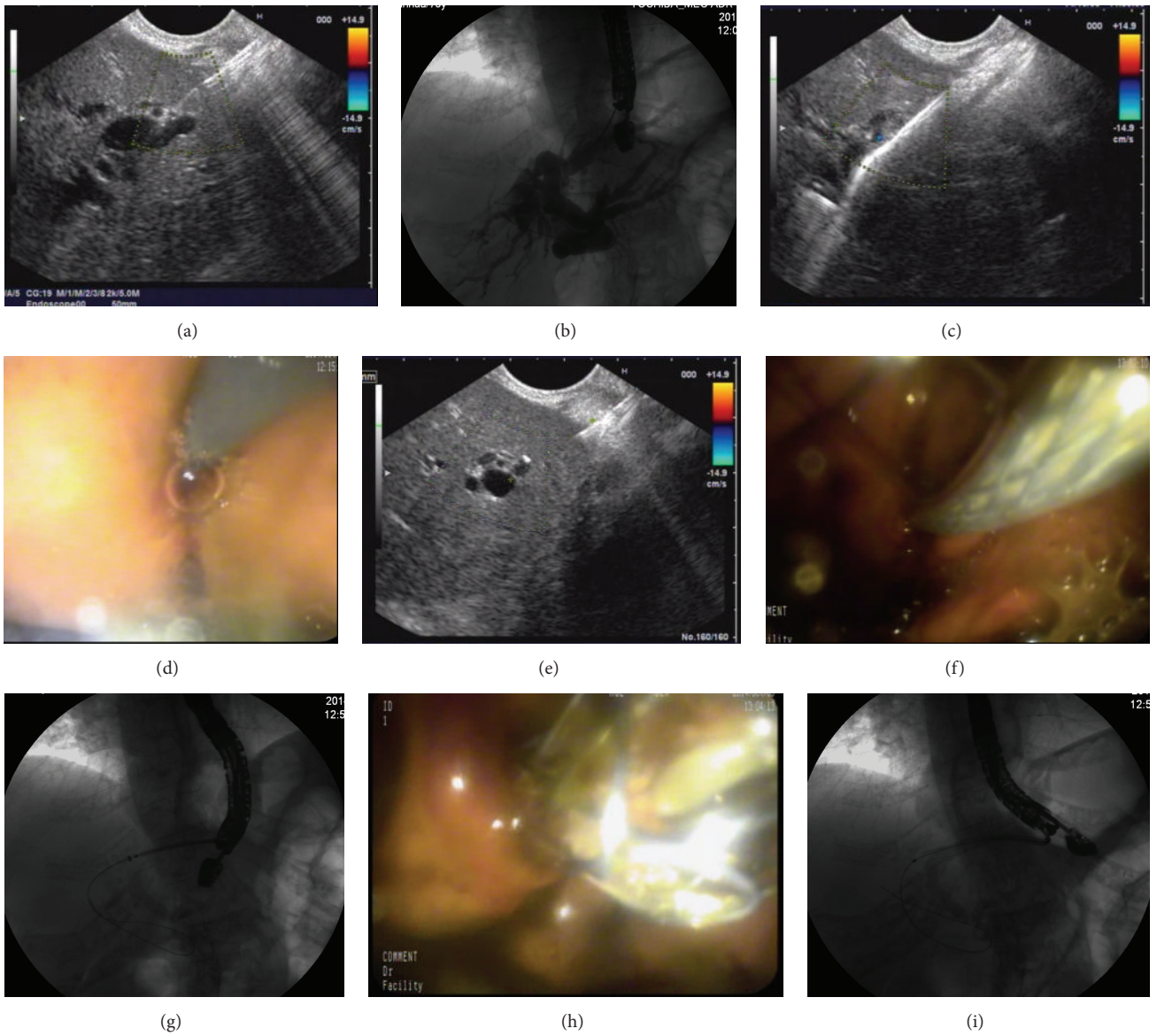

Figure 1: (a) Echoendoscope was advanced into the stomach. After checking local vasculature with color Doppler, the EUS puncture needle was then advanced into the intrahepatic duct. (b) Cholangiography was performed, which usually delineates the dilated biliary tree down to the point of obstruction. (c) A guidewire was then inserted through the needle. (d) The cystotome was used to create a fistula between the stomach and the left hepatic duct. (e) The distance between the stomach and the left hepatic duct was measured. (f)–(i) Once the fistula has been dilated, a fully covered SEMS (10 mm diameter × 8 cm length, fully covered with a silicon membrane) was inserted and deployed transmurally.

Complications after EUS-BD include pneumoperitoneum, bile leakage, cholangitis, bleeding, abdominal pain, and stent occlusion. Gupta et al. [28] compared the complication rates of EUS-BD in patients with benign and malignant diseases and found similar complication rates in both groups (26.7% versus 37.1%). They placed stents in 173 patients with malignant etiologies, including 42 (24%) plastic and 131 (76%) metal stents, and found no significant difference in complication rates between the two types of stents but did note a trend towards better outcomes in patients with metal stents ($P = 0.09$).

EUS-BD was initially largely performed using plastic stents, though many experts reported favorable outcomes with SEMS, instead of plastic stents [29–31]. Song et al. [32] performed a study in 15 patients with distal malignant biliary obstruction who were candidates for alternative techniques of biliary decompression following failed ERCP. They achieved a technical success rate following EUS-CDS with a fully covered SEMS of 86.7% (13/15), and a functional success rate of 100% (13/13). Eum et al. [30] studied three consecutive patients who underwent EUS-BD with a fully covered SEMS for biliary decompression and concluded that this technique

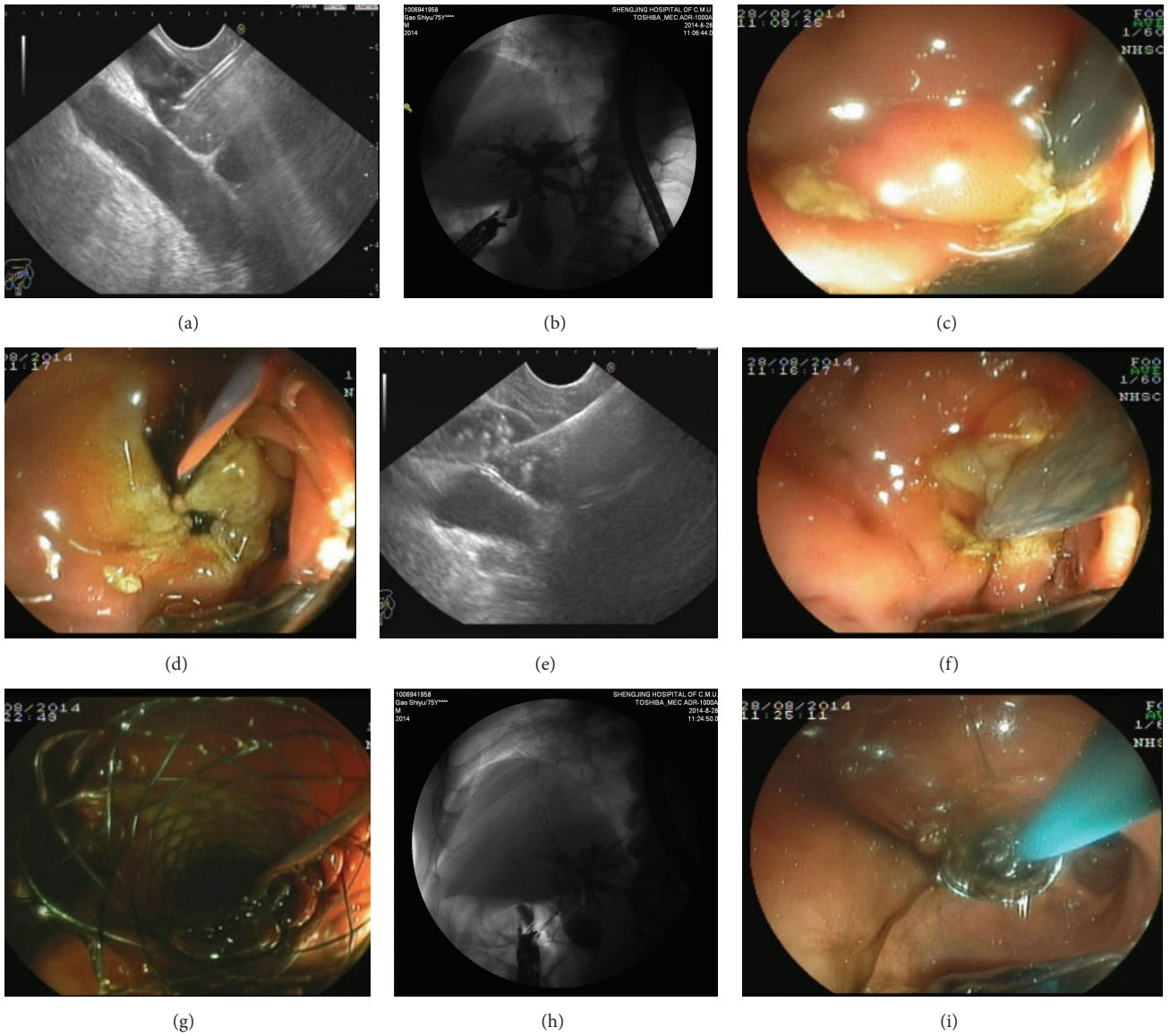

Figure 2: (a) Echoendoscope was advanced into the duodenal bulb. After checking local vasculature with color Doppler, the EUS puncture needle was then advanced into the intrahepatic duct. (b) Cholangiography was performed, which usually delineates the dilated biliary tree down to the point of obstruction. (c) The cystotome was used to create a fistula between the stomach and the left hepatic duct. (d) The puncture site after dilation. (e) The guidewire was observed under the EUS. (f)–(h) The fully covered SEMS was inserted and deployed transmurally. (i) To avoid bile leakage into the peritoneum, a 7 Fr nasobiliary was placed through the metallic stent.

was able to achieve a large-diameter sustainable fistula. Endoscopic intervention through this fistula thus seems to be feasible and useful for the management of intrabiliary lesions. Fabbri et al. [20] successfully used a new partially covered biliary stent for EUS-assisted cholangiography in patients with malignant biliary obstruction. There were no major complications or procedure-related deaths, and no patients required endoscopic reintervention during the 170-day follow-up period.

We used fully covered SEMS in the current study. These stents may decrease the risk of bile leakage and pneumoperitoneum. Indeed, only one patient suffered from bile leakage (4.8%, 1/21), which occurred in the primary stage of treatment and may have been related to lack of experience of the procedure. The resulting peritonitis was mild and self-limited.

CDS or HGS is used for gastrointestinal luminal access, depending on the desired site. In our study, EUS-HGS was usually performed in patients suffering from proximal bile duct obstruction, surgically altered anatomy, or duodenal-bulb invasion. We found no difference in efficacy between HGS and CDS. Artifon et al. [22] compared the outcomes of EUS-CDS and EUS-HGS in 49 patients with unresectable distal malignant biliary obstruction and failed ERCP. The technical success rates for HGS and CDS were 96% and 91%, and the clinical success rates were 91% and 77%, respectively.

The mean procedural times were 47.8 min for HPG and 48.8 min for CDS. The mean quality of life scores were similar during follow-up. They therefore concluded that HGS and CDS were similar in terms of efficacy and safety.

EUS-guided rendezvous is a choice for the patient after failed ERCP with issues of biliary cannulation at the papilla. Compared with direct transluminal techniques, the process of rendezvous is relatively complex and time consuming. In the study of Khashab et al. [6], 35 patients underwent EUS-BD (rendezvous $n = 13$, transluminal $n = 20$). Technical success was achieved in 33 patients (94%), and clinical success was attained in 32 of 33 patients (97.0%). There was no significant difference in adverse event rate between rendezvous and transluminal groups (15.4% versus 10%; $P = 0.64$). In their study, both rendezvous and direct transluminal techniques seem to be equally effective and safe. So, we always choose direct transluminal techniques instead.

In the current study, four of the 21 patients died after about 13 months of follow-up; however, the fully covered SEMS was still functioning after the time span it would be expected to remain in patients with unresectable malignancies.

One disadvantage of fully covered SEMS is their greater cost, compared with plastic stents. However, their long-term patency and significantly lower reintervention rates suggest that metal stents may still represent a cost-effective choice.

In summary, EUS-BD with fully covered SEMS offers great potential as an alternative method of biliary decompression, associated with high success rates, low complication rates, and a lack of fatalities. The present study was limited by its retrospective nature and relatively small sample size. Larger prospective studies are thus needed to confirm these results.

Competing Interests

The authors declare that they have no competing interests.

References

[1] P. Kedia, M. Gaidhane, and M. Kahaleh, "Endoscopic guided biliary drainage: how can we achieve efficient biliary drainage?" *Clinical Endoscopy*, vol. 46, no. 5, pp. 543–551, 2013.

[2] V. E. Ekkelenkamp, R. A. De Man, F. Ter Borg et al., "Prospective evaluation of ERCP performance: results of a nationwide quality registry," *Endoscopy*, vol. 47, no. 6, pp. 503–507, 2015.

[3] T. H. Baron, B. T. Petersen, K. Mergener et al., "Quality indicators for endoscopic retrograde cholangiopancreatography," *Gastrointestinal Endoscopy*, vol. 63, no. 4, pp. S29–S34, 2006.

[4] E. C. S. Lai, K. M. Chu, C.-Y. Lo et al., "Surgery for malignant obstructive jaundice: analysis of mortality," *Surgery*, vol. 112, no. 5, pp. 891–896, 1992.

[5] A. B. Winick, P. N. Waybill, and A. C. Venbrux, "Complications of percutaneous transhepatic biliary interventions," *Techniques in Vascular and Interventional Radiology*, vol. 4, no. 3, pp. 200–206, 2001.

[6] M. A. Khashab, A. K. Valeshabad, R. Modayil et al., "EUS-guided biliary drainage by using a standardized approach for malignant biliary obstruction: rendezvous versus direct transluminal techniques (with videos)," *Gastrointestinal Endoscopy*, vol. 78, no. 5, pp. 734–741, 2013.

[7] J. N. Shah, F. Marson, F. Weilert et al., "Single-operator, single-session EUS-guided anterograde cholangiopancreatography in failed ERCP or inaccessible papilla," *Gastrointestinal Endoscopy*, vol. 75, no. 1, pp. 56–64, 2012.

[8] M. S. Bhutani and A. Arora, "New developments in endoscopic ultrasound-guided therapies," *Endoscopic Ultrasound*, vol. 4, no. 4, pp. 304–311, 2015.

[9] D. H. Park, J. W. Jang, S. S. Lee, D.-W. Seo, S. K. Lee, and M.-H. Kim, "EUS-guided biliary drainage with transluminal stenting after failed ERCP: predictors of adverse events and long-term results," *Gastrointestinal Endoscopy*, vol. 74, no. 6, pp. 1276–1284, 2011.

[10] M. Giovannini, V. Moutardier, C. Pesenti, E. Bories, B. Lelong, and J. R. Delpero, "Endoscopic ultrasound-guided bilioduodenal anastomosis: a new technique for biliary drainage," *Endoscopy*, vol. 33, no. 10, pp. 898–900, 2001.

[11] M. Giovannini, M. Dotti, E. Bories et al., "Hepaticogastrostomy by echo-endoscopy as a palliative treatment in a patient with metastatic biliary obstruction," *Endoscopy*, vol. 35, no. 12, pp. 1076–1078, 2003.

[12] A. Püspök, F. Lomoschitz, C. Dejaco, M. Hejna, T. Sautner, and A. Gangl, "Endoscopic ultrasound guided therapy of benign and malignant biliary obstruction: a case series," *The American Journal of Gastroenterology*, vol. 100, no. 8, pp. 1743–1747, 2005.

[13] M. Kahaleh, A. J. Hernandez, J. Tokar, R. B. Adams, V. M. Shami, and P. Yeaton, "Interventional EUS-guided cholangiography: evaluation of a technique in evolution," *Gastrointestinal Endoscopy*, vol. 64, no. 1, pp. 52–59, 2006.

[14] U. Will, A. Thieme, F. Fueldner, R. Gerlach, I. Wanzar, and F. Meyer, "Treatment of biliary obstruction in selected patients by endoscopic ultrasonography (EUS)-guided transluminal biliary drainage," *Endoscopy*, vol. 39, no. 4, pp. 292–295, 2007.

[15] E. Bories, C. Pesenti, F. Caillol, C. Lopes, and M. Giovanni, "Transgastric endoscopic ultrasonography-guided biliary drainage: results of a pilot study," *Endoscopy*, vol. 39, no. 4, pp. 287–291, 2007.

[16] A. Y. Altonbary, A. G. Deiab, and M. H. Bahgat, "Endoscopic ultrasound-guided choledechoduodenostomy for palliative biliary drainage of obstructing pancreatic head mass," *Endoscopic Ultrasound*, vol. 3, no. 2, pp. 137–140, 2014.

[17] M. A. Khashab and S. Varadarajulu, "Endoscopic ultrasonography as a therapeutic modality," *Current Opinion in Gastroenterology*, vol. 28, no. 5, pp. 467–476, 2012.

[18] M. A. Khashab, A. K. Valeshabad, E. Afghani et al., "A comparative evaluation of EUS-guided biliary drainage and percutaneous drainage in patients with distal malignant biliary obstruction and failed ERCP," *Digestive Diseases and Sciences*, vol. 60, no. 2, pp. 557–565, 2015.

[19] B. C. Brauer, Y. K. Chen, N. Fukami, and R. J. Shah, "Single-operator EUS-guided cholangiopancreatography for difficult pancreaticobiliary access (with video)," *Gastrointestinal Endoscopy*, vol. 70, no. 3, pp. 471–479, 2009.

[20] C. Fabbri, C. Luigiano, L. Fuccio et al., "EUS-guided biliary drainage with placement of a new partially covered biliary stent for palliation of malignant biliary obstruction: a case series," *Endoscopy*, vol. 43, no. 5, pp. 438–441, 2011.

[21] V. Dhir, S. Bhandari, M. Bapat, and A. Maydeo, "Comparison of EUS-guided rendezvous and precut papillotomy techniques for

biliary access (with videos)," *Gastrointestinal Endoscopy*, vol. 75, no. 2, pp. 354–359, 2012.

[22] E. L. A. Artifon, F. P. Marson, M. Gaidhane, M. Kahaleh, and J. P. Otoch, "Hepaticogastrostomy or choledochoduodenostomy for distal malignant biliary obstruction after failed ERCP: is there any difference?" *Gastrointestinal Endoscopy*, vol. 81, no. 4, pp. 950–959, 2015.

[23] K. Hara, K. Yamao, S. Hijioka et al., "Prospective clinical study of endoscopic ultrasound-guided choledochoduodenostomy with direct metallic stent placement using a forward-viewing echoendoscope," *Endoscopy*, vol. 45, no. 5, pp. 392–396, 2013.

[24] K. Hara, K. Yamao, Y. Niwa et al., "Prospective clinical study of EUS-guided choledochoduodenostomy for malignant lower biliary tract obstruction," *The American Journal of Gastroenterology*, vol. 106, no. 7, pp. 1239–1245, 2011.

[25] T. Iwashita, J. G. Lee, S. Shinoura et al., "Endoscopic ultrasound-guided rendezvous for biliary access after failed cannulation," *Endoscopy*, vol. 44, no. 1, pp. 60–65, 2012.

[26] Y. S. Kim, K. Gupta, S. Mallery, R. Li, T. Kinney, and M. L. Freeman, "Endoscopic ultrasound rendezvous for bile duct access using a transduodenal approach: cumulative experience at a single center: a case series," *Endoscopy*, vol. 42, no. 6, pp. 496–502, 2010.

[27] D. H. Park, S. U. Jeong, B. U. Lee et al., "Prospective evaluation of a treatment algorithm with enhanced guidewire manipulation protocol for EUS-guided biliary drainage after failed ERCP (with video)," *Gastrointestinal Endoscopy*, vol. 78, no. 1, pp. 91–101, 2013.

[28] K. Gupta, M. Perez-Miranda, M. Kahaleh et al., "Endoscopic ultrasound-assisted bile duct access and drainage: multicenter, long-term analysis of approach, outcomes, and complications of a technique in evolution," *Journal of Clinical Gastroenterology*, vol. 48, no. 1, pp. 80–87, 2014.

[29] E. L. A. Artifon, A. V. Safatle-Ribeiro, F. C. Ferreira et al., "EUS-guided antegrade transhepatic placement of a self-expandable metal stent in hepatico-jejunal anastomosis," *Journal of the Pancreas*, vol. 12, no. 6, pp. 610–613, 2011.

[30] J. Eum, D. H. Park, C. H. Ryu et al., "EUS-guided biliary drainage with a fully covered metal stent as a novel route for natural orifice transluminal endoscopic biliary interventions: a pilot study (with videos)," *Gastrointestinal Endoscopy*, vol. 72, no. 6, pp. 1279–1284, 2010.

[31] L. H. Lai, F. K. L. Chan, J. J. Y. Sung, A. W. H. Chan, and K. F. Lee, "EUS-guided transduodenal biliary drainage," *Gastrointestinal Endoscopy*, vol. 72, no. 1, pp. 186–187, 2010.

[32] T. J. Song, Y. S. Hyun, S. S. Lee et al., "Endoscopic ultrasound-guided choledochoduodenostomies with fully covered self-expandable metallic stents," *World Journal of Gastroenterology*, vol. 18, no. 32, pp. 4435–4440, 2012.

Hindawi Publishing Corporation
Gastroenterology Research and Practice
Volume 2016, Article ID 3432640, 9 pages
http://dx.doi.org/10.1155/2016/3432640

Review Article

Risk and Surveillance of Cancers in Primary Biliary Tract Disease

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Received 21 January 2016; Revised 14 April 2016; Accepted 18 May 2016

Academic Editor: Kerstin Schütte

Primary biliary diseases have been associated in several studies with various malignancies. Understanding the risk and optimizing surveillance strategy of these malignancies in this specific subset of patients are an important facet of clinical care. For instance, primary sclerosing cholangitis is associated with an increased risk for cholangiocarcinoma (which is very challenging to diagnose) and when IBD is present for colorectal cancer. On the other hand, primary biliary cirrhosis patients with cirrhosis or not responding to 12 months of ursodeoxycholic acid therapy are at increased risk of hepatocellular carcinoma. In this review we will discuss in detail the risks and optimal surveillance strategies for patients with primary biliary diseases.

1. Introduction

Primary biliary diseases encompass several entities including primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH), and overlap syndrome (classified as having PBC, PSC, or AIH). Patients affected with these diseases often present with a cholestatic biochemical profile and often are asymptomatic. Distinction between these entities is necessary due to variance of associated complications and recommended management. Complications of biliary diseases include an increased risk for development of malignancy especially in certain subsets of patients. In this review we intend to shed a light on advances in diagnosis and management of malignancy in patients with primary biliary diseases.

2. Overlap Syndromes

The serologic and clinical characteristics of AIH may overlap with other forms of chronic immune-mediated liver disorders such as PBC and PSC. Although the prevalence of overlap syndromes is small, it may affect the management and prognosis of patient's illness. The International AIH Group (IAIHG) recommends that patients with suspected overlap syndrome be classified on the basis of their primary disease as AIH, PBC, or PSC and therapy of primary disease should determine therapy [1]. A synopsis of the PBC-AIH and PSC-AIH overlap syndromes is as follows.

2.1. PSC-AIH Overlap. On the basis of criteria deemed arbitrary by the IAIHG, the frequency of PSC-AIH overlap ranges from 6% to 11% [2]. The hallmark of this overlap syndrome is the serologic finding reflective of AIH (presence of ANA and/or ASMA) and radiographic finding reflective of PSC. One study reported that PSC-AIH overlap patients had higher serum globulins ($P = 0.01$), IgG levels ($P = 0.001$), autoantibody titers ($P < 0.001$), and histologic scores ($P < 0.001$) than patients with PSC alone [3]. If a patient with known inflammatory bowel disease (particularly, ulcerative colitis) presents with pruritus, has an elevated alkaline phosphatase, and demonstrates radiographic or histologic findings of PSC, a diagnosis of PSC-AIH overlap can be considered. This overlap syndrome is difficult to treat. Although the safety and efficacy of immunosuppressive treatment are established in AIH, no effective therapy exists for PSC. A combination of immunosuppression (such as azathioprine)

and varying doses of ursodiol may be tried; one study reported the efficacy of this regimen to be 20%–100% with inverse relationship to the severity of cholestasis. In selected patients, empiric cyclosporin, mycophenolate mofetil, and budesonide were also found to be beneficial [2].

2.2. PBC-AIH Overlap. One study reported the frequency of this overlap syndrome to be 7%–13% and reported the patients to be highly susceptible to a variety of autoimmune and immunologic diseases [2]. Two varieties of PBC-AIH overlap exist, based on presence or absence of antimitochondrial antibodies (AMAs). The AMA-positive variety of PBC-AIH overlap demonstrates histologic characteristics of AIH and responds well to steroid therapy. On the other hand, the AMA-negative variety of PBC-AIH overlap is usually positive for antinuclear antibodies (ANA) and/or antismooth muscle antibodies (ASMA) and has histologic findings and therapeutic management consistent with PBC. The AMA-negative variety of PBC-AIH overlap has also been termed "autoimmune cholangitis" or "immune cholangiopathy" and could also be considered as an AMA-negative form of PBC. The diagnostic criteria of the PBC-AIH overlap have garnered significant interest among gastroenterology circles. One of such diagnostic criteria, termed Paris criteria, requires the presence of two out of three diagnostic criteria for each of PBC and AIH to denote a case as PBC-AIH overlap. Accepted diagnostic criteria of PBC and AIH under Paris criteria are as follows:

Accepted criteria for diagnosis of PBC:

(1) Twofold elevation in the alkaline phosphatase or fivefold elevation in the γ-glutamyl transferase.

(2) Positive AMA.

(3) Liver biopsy with bile duct lesions as seen in PBC.

Accepted criteria for diagnosis of AIH:

(1) Elevated ALT of at least fivefold the upper limit of normal.

(2) At least a twofold increase in IgG level or a positive ASMA.

(3) A liver biopsy with classic findings suggestive of AIH.

Paris criteria yield high diagnostic accuracy with sensitivity and specificity of 92% and 97%, respectively [4].

PBC-AIH overlap syndrome responds well to a combination of immunosuppression (such as azathioprine) and ursodiol [1, 2, 4]. We learn the following lessons:

(i) Overlap syndrome could be classified as encompassing AIH and either PBC or PSC.

(ii) AMA-positive AIH-PBC overlap demonstrates histologic characteristics of AIH and responds well to steroid therapy.

(iii) AMA-negative variety of AIH-PBC overlap is positive for ANA and/or ASMA and should be managed as PBC.

(iv) AIH-PSC overlap is difficult to treat.

3. Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a cholestatic liver disease often affecting men (male : female, 2 : 1) in their fifties and is commonly associated with inflammatory bowel disease (IBD) [5, 6].

The pathogenesis of PSC remains obscure and is thought to involve (similar to PBC) several pathways that include autoimmune, genetic, and infectious processes. Evidence for an autoimmune component is underlined by its association with many extrahepatic autoimmune diseases. On the other hand, GWAS studies have revealed several genetic loci associated with an increased risk for development of PSC.

3.1. Risk of Malignancy. PSC is considered a premalignant condition. Risk for cholangiocarcinoma (CCA) and colon cancer and in cirrhotic patients risk for hepatocellular carcinoma are increased. CCA accounts for about 15% of primary liver and intrahepatic bile duct cancers annually in the United States with an incidence of 1-2 per 100,000 persons [7–9].

In a Swedish study by Bergquist et al., 44% of deaths in their cohort of patients were related to malignancies. It was determined that in their cohort of 604 PSC followed for 5.7 years the incidence of hepatobiliary carcinoma was 1.5% per year and cholangiocarcinoma was 13%. Most importantly, pancreatic carcinoma risk was found to be 14 times higher compared with the general population and malignancy can affect up to 25% of the patients with PSC [10].

The presence of dominant stenosis/strictures (defined as a stricture less than 1.5 mm diameter in the common bile duct or less than 1 mm in the left or right main hepatic ducts) when accompanied with IBD seems to be associated with an increased risk of cancers including biliary, gallbladder, and colorectal malignancies as compared to those without preexistent IBD. This may suggest that patients with dominant stenosis may represent a sicker group of people with worsened outcomes [11].

There is a widely accepted sequence in development of CCA in PSC inflammation-dysplasia-carcinoma. Neither of other suggested predictors as elevated Bilirubin, variceal bleeding, older age, and duration of IBD was found to be clinically useful. CCA develops independently of cirrhosis. A study performed at the Mayo Clinic demonstrated that inducible nitric oxide (iNOS) is expressed in PSC and CCA but not in normal biliary epithelium and increases in 8-oxodeoxyguanosine. These findings with generation of oxysterols in bile support inflammatory theory of pathogenesis [12]. Signaling has been implicated in biliary cancers such as CCA in patients with PSC [13–17]. Genetic polymorphism of natural killer cell receptor G2D (NKG2D) is seen to be a risk factor for these patients [18], as well as loss of CDKN2A/p16 gene at the chromosome 9p21 locus which is a marker for dysplasia [19].

PSC is the most common risk factor for developing CCA in the Western countries [20]. CCA can be found in 5–15% of patients with PSC [21, 22] with the annual incidence rate of 0.6–1.5% and lifetime risk of 7 to 20% [5, 23]. The prognosis for CCA is very poor with median survival time of 5 months after diagnosis [24].

A study from Finland utilizing 20 years of follow-up reports almost 1000-fold risk of CCA in concomitant IBD and PSC compared to the general population [25]. More than a third of the patients with PSC are expected to be diagnosed with CCA within the first year of having PSC, with most CCAs being found in the first 2.5 years after the conclusion of PSC [23]. Furthermore, a study evaluating autopsy findings estimated the occurrence of CCA in patients with PSC at 40% [26, 27].

Due to lack of sensitive diagnostic testing, distinction between benign bile duct strictures and CCA remains challenging. Serological testing is of importance in making that distinction. Tumor marker CA 19-9 with a serum level higher than 100 IU/mL has 75% sensitivity and 80% specificity in identifying CCA in patients with PSC. Accuracy can be improved to 86% by addition of CEA [28]. Increasing the CA 19-9 cut-off level to >129 IU/mL in one study has improved specificity to 99% but only in the absence of bacterial infection [29].

Combining serological and imaging techniques may yield increased sensitivity and specificity for diagnosis of CCA in PSC. In an observational study aiming at evaluating the role of combinations of serological testing and imaging in detecting CCA in patients with PSC it was determined that CA 19-9 combined with one of ultrasonography, computed tomography, or magnetic resonance imaging provided a sensitivity of 91%, 100%, and 96%, specificity of 62%, 38%, and 37%, PPV of 23%, 22%, and 24%, and NPV of 98%, 100%, and 98%, respectively [30].

It is worth noting that elevated serum biomarker may carry a prognostic utility following tumor resection. Such utility has been demonstrated in patients with pancreatic adenocarcinoma where CA 19-9 was predictive of postresection survival [31].

Nonetheless, bile duct brushings during ERCP remain first-line investigative procedure for biliary strictures, which also helps palliate dominant strictures. However, sensitivity yield remains low at around 40–50%. American Society of Gastrointestinal Endoscopy recommends > 5 passes across the stricture, removal of brush and catheter together, and inclusion of washing into the specimen to increase diagnostic yield of the test [32]. Cleveland Clinic uses two sets of brushings: one for cytology and one for FISH [33]. One small sized Japanese study reports achieving 100% specificity with forceps biopsy [34].

Fluorescence in situ hybridization (FISH) is used to reveal chromosomal abnormality by fluorescence-labeled probes. There are four commercially available FISH probes which bind to chromosomes 3, 7, 17, and 9p21 locus, responsible for p16 tumor suppressor gene. Obvious advantages of FISH as compared to endoscopic testing are the lack of interobserver variability and simplicity. One of the main concerns regarding the application of FISH in early detection of CCA in the patients with PSC is the modest sensitivity and can be considered exclusively in patients with a high pretest probability [35].

A meta-analysis conducted by Navaneethan et al. found that pooled sensitivity and specificity for FISH test using polysomy alone as a positive result for the diagnosis of CCA in PSC patients were 51% (95% CI: 43%–59%) and 93% (95% CI: 91–95%), but low likelihood ratios (positive at 6.51 and negative at 0.56) do not allow using FISH as a single test in diagnosing CCA with PSC patients [36]. Patients with CCA associated with PSC have higher (80%) prevalence of DNA aneuploidy than those with PSC and without CCA [37].

Eaton et al. further evaluated the opportunities provided by fluorescence in situ hybridization [38]. They concluded that multifocal polysomy detected by the FISH in multiple areas of biliary tree is the strongest predictor of CCA diagnosis among PSC patients suspected of having biliary cancer.

A recent analysis of biliary brush samples for DNA methylation of certain genes identified four genes: CDO1, CNRIP1, SEPT9, and VIM. Use of these genes as a panel displayed 85% sensitivity and 98% specificity in early detection of CCA in PSC patients [39].

One of the last trends in noninvasive diagnosis of malignant biliary strictures is measurement of "Volatile Organic Compounds" in bile or urine. A study from Cleveland Clinic reported the utility of ethane, 2-propanol, trimethylamine, carbon disulfide, and 1-octene levels as predictors of biliary malignancy in PSC patients [40].

Another interesting approach in diagnosing CCA in patients with PSC is the analysis of miRNA patterns in serum and bile. Several miRNAs occur at lower concentrations in CCA compared to PSC patient without CCA. The most promising miRNA in the serum in this regard was miR-126 with specificity of 93% [41].

Another technique is analysis of bile and serum peptides with capillary electrophoresis coupled with mass spectrometry. This allows for discrimination between PSC with CCA and absence of CCA with 84% sensitivity [42]. Lankisch et al. propose using urine to obtain bile instead of utilizing invasive and time-consuming endoscopic procedures.

Novel diagnostic modalities have been introduced recently; these, however, carry a disadvantage of the results being operator-dependent. One such modality is intraductal ultrasonography (IDUS) which can be performed as a part of routine ERCP without the need of sphincterotomy. This technique, however, does not provide histopathology limiting its use to an adjunct diagnostic tool despite its reasonably good sensitivity and specificity, especially in the proximal biliary strictures [43].

On the other hand, cholangioscopy has a specificity of 82–90% which is even higher with visual targeted biopsy [33, 44, 45]. However, the value of the visualization without clinical correlation limits the utility of this method for surveillance of dominant stenosis [43, 46]. Another limiting factor is the associated complications related to the need of performing a sphincterotomy to conduct the test. Serious procedure-related adverse events of cholangioscopy have been reported at around 7.5% [44]. Other complications may occur with tight distal strictures where the rate of postprocedural cholangitis is reported at 11% [47].

Narrow Band Imaging is another modality which provides improved visualization. One study reported increased detection of suspicious lesions which was not confirmed by dysplasia detection [48]. Probe based confocal laser

endomicroscopy (pCLE) detects neovascularization and abnormal vessels in biliary strictures. This technique has been proposed as a method with high technical success in patients with PSC for exclusion of CCA with high sensitivity and negative predictive value [49]. This method, however, has a reported specificity of only 61%. However, introduction of the Miami classification and Paris inflammatory criteria may help improve specificity [50]. Meining et al. described an increase in accuracy by addition of pCLE to ERCP when compared to ERCP and tissue sampling alone [51]. This may also carry the advantage of reducing the frequency of tissue samplings in patients with PSC and dominant strictures during evaluation for CCA. Widespread use of this technology is limited by the need for specialized operator training and low specificity [46].

3.2. Surveillance. Diagnosis of CCA in PSC may be very challenging and may sometimes require rather invasive techniques as discussed above. Hence, no accepted surveillance strategy for CCA in PSC is currently present.

Because sensitivity and accuracy of the biliary brushings with FISH are still debatable and these tests may carry certain risks for complications from ERCP (such as pancreatitis and cholangitis) this method is not recommended for surveillance at this point but is very useful for diagnosis.

Recommendations for offering testing of liver enzymes every 6 months with an annual check of CA 19-9 plus any of the imaging studies available (MRCP, US, and CT cholangiography) have been previously suggested [20]. In the cases of dominant stenosis or any suspicion indicating the need to proceed with ERCP, bile brushings and FISH are anticipated.

3.3. Colorectal Cancer. Colorectal cancer (CRC) is annually diagnosed in 134,490 men and women in the United States [52]. Some early studies suggested that the prevalence of CRC in the setting of concomitant PSC and ulcerative colitis (UC) is around 9–14% in the first 10 years of establishing a combined diagnosis, 31% at 20 years, and up to 50% at 25 years [53].

In a study looking at risk of cancers in patients with PSC and inflammatory bowel disease, the authors reported an increased risk for CRC with odds ratio of 5 (95% CI: 2.80–8.95) [54]. The finding of increased risk for CRC in PSC-UC patients was also reported in a meta-analysis of eleven studies [55].

Hence, current guideline recommendations [5] are to perform screening colonoscopy with biopsy at diagnosis of PSC and then every 5 years if no IBD is present and yearly if IBD is present [53, 56–60].

3.4. Gallbladder Carcinoma. Gallbladder cancer has an incidence of 1 to 2 cases per 100,000 persons in the US [61]. Patients with PSC are at increased risk of gallbladder carcinoma. A study of 102 PSC patients undergoing cholecystectomy revealed a 13.7% occurrence of gallbladder lesions with greater than 50% of these lesions being malignant [62]. Hence, current guidelines recommend annual surveillance for gallbladder lesions with U/S [5].

3.5. Hepatocellular Carcinoma. A German study aimed at evaluating the risk of HCC in more than 500 PSC patients did not show increased risk of HCC in this subset of patients [63]. We learn the following lessons:

(i) PSC carries an increased risk for cholangiocarcinoma (CCA) and colon cancer and in cirrhotic patients for hepatocellular carcinoma.

(ii) The annual incidence rate of CCA is reported to be 0.6–1.5% with a lifetime risk of 7 to 20%.

(iii) Diagnosis of CCA in PSC may is very challenging.

(iv) PSC-UC involves a dramatic increased risk of CRC.

(v) Perform screening colonoscopy with biopsy at diagnosis of PSC and then every 5 years if no IBD is present and yearly if IBD is present.

4. PBC

PBC is a rare chronic cholestatic liver disease that, if left untreated, eventually culminates in cirrhosis and liver failure. The exact pathogenesis of PBC remains under investigation. One of the proposed mechanisms includes the obliteration of small intralobular bile ducts through T-lymphocyte-mediated activity. Other proposed mechanisms involve environmental, geographic, and genetic factors.

Evidence for underlying autoimmune disease is supported by the presence of circulating antibodies and elevated immunoglobulins on serology, association with other autoimmune conditions, and development of granulomas in patients with PBC.

Environmental factors have been implicated by studies such as the one published by Prince et al. and McNally et al. that sought to describe the temporal and spatial distribution of PBC within defined geographical areas. PBC was found to be significantly more prevalent in urban areas when compared to rural locales [64]. Moreover, areas with higher levels of socioeconomic deprivation had an increased risk of PBC ($P = 0.035$) in McNally's study. Spatial clustering of PBC cases was also confirmed in this study [65].

Additionally, Muirhead et al. discovered that PBC demonstrated a temporal pattern suggesting a possible role of seasonal factors affecting the disease [66].

Genome Wide Association Studies (GWAS) in PBC have further solidified a role of a genetic component and have been instrumental in advancement of our knowledge in the pathogenesis of PBC. According to a review by Gulamhusein et al., there have been six large scale studies which have identified 27 risk loci in addition to HLA associated with PBC [67]. Two such studies published by Underhill et al. revealed an association between PBC and human major histocompatibility complex (HLA) DR8 and DPB subgroup [68, 69]. Another study published by Wang et al. described increased frequency of circulating T follicular helper (Tfh) cells in PBC patients. Additionally, this study described a decrease in Tfh cells in patients using ursodeoxycholic acid (UDCA) [70]. This study was reinforced by Limongi's findings which demonstrated a significant reduction of T-helper 1 cytokines after treatment with UDCA [71].

Some studies also indicate that infectious processes may play a role in the progression of PBC. Some of the implicated infections include *Chlamydia pneumoniae*, *E. coli* (particularly UTI caused by *E. coli*), and *Lactobacillus*. To further establish an infectious role to the progression of PBC, Thomas et al. demonstrated that zidovudine was associated with a significant reduction in alkaline phosphatase as well as cholangitis and ductopenias at 12 months. Other studies detailed in that same paper described promising trials using the combination of tenofovir and emtricitabine and lopinavir [72].

4.1. Risk of Malignancy. Several studies have indicated that patients with PBC are at increased risk for specific malignancies such as hepatocellular carcinoma.

Cirrhotic PBC patients are at increased risk of hepatocellular carcinoma (HCC). A study in the Greek population of PBC patients revealed a 10-year risk of 4% for developing HCC (15% in cirrhotic patients) and of 13% for developing extrahepatic malignancies [73]. A similar study in Spanish and Italian populations revealed that the prevalence and incidence (0.35 and 0.37 per 100 patient-years in Barcelona and Padova accordingly) of HCC were similar. Only advanced histological stage was associated with around a sixfold risk of development of HCC (odds ratio [OR]: 5.80, 95% confidence interval [CI]: 2.34–14.38, $P < 0.001$). On the other hand, male gender, age >52 years, smoking, alcohol >40 g/day, presence of HBsAg, and anti-HCV were not associated with HCC [74]. Unlike cryptogenic and alcoholic cirrhosis, obesity does not appear to be an independent risk factor for development of HCC in PBC patients [75].

A recent study by Boonstra et al. involving 992 PBC patients followed for a median of 73 months (range: 0–434) concluded that there was a ninefold increased risk of developing hepatobiliary malignancies (incidence ratio: 9.4; 95% CI: 3.04–21.8) [76]. The risk for developing HCC was also confirmed in a 2012 meta-analysis by Liang et al. which revealed that patients with PBC have a relative risk of 19 (95% CI: 11–27) as compared to the general population for developing HCC [77].

A recent international multicenter study revealed that 12-month biochemical nonresponse in patients with PBC on ursodeoxycholic acid was associated with increased risk of developing HCC [78].

Conflicting evidence regarding increased risk of breast cancer or lack thereof has been published [79–83]. On the other hand, Boonstra et al. revealed that patients with PBC have a fivefold increase in risk for developing urinary bladder cancer (SIR 5.0; 95% CI: 1.6–11.6) and 1.8-fold increase in risk for developing breast cancer (SIR 1.8; 95% CI: 1.0–2.81) [76]. We learn the following lessons:

(i) Cirrhotic PBC patients are at increased risk of hepatocellular carcinoma (HCC).

(ii) 12-month biochemical nonresponse in patients with PBC on ursodeoxycholic acid was associated with increased risk of developing HCC.

(iii) There is conflicting evidence regarding increased risk of breast cancer in PBC patients.

4.2. AIH. AIH is characterized by high globulin levels, autoimmune features, and circulating antibodies directed against self; AIH is a chronic inflammation of the liver that can progress to cirrhosis. Due to the variety of ways AIH can manifest, various immunogenic phenotypes, circulating autoantibodies, and clinical features have been used to characterize the disease process. Among the modalities used to describe this disease process, classification using circulating autoantibodies has been suggested but has not been that effective given the lack of evidence that ties these antibodies to the pathogenesis of AIH.

One of the major theories for the pathogenesis of AIH proposes a combination of environmental triggers (which includes viruses, herbal supplementations, medications, and immunizations) in a patient who is genetically predisposed. Despite lack of evidence regarding detailed associations between antigens, genetic predisposition, and the autoimmune process, the biomolecular level is thought to involve interaction between antigen, MHC, and T-cell receptors forming a complex that serves as a contact point to induce autoimmunity. However, the exact inducers of autoimmunity cannot be specified. It is also reported that change in T-cell function plays a central role in the pathogenesis of AIH with loss of tolerance via absence of normal suppression of self-reactive T-cells, with B cell abnormalities playing a lesser role. This mechanism of loss of tolerance contributes to repetitive inflammation and necrosis of liver in AIH. The immunoglobulin superfamily which also include HLA class within the MHC, immunoglobulins, and T-cell receptor molecules have been the targets with ongoing research to identify genetic predisposing factors. The HLA-DR3 serotype has a strong presence in Caucasians with type I AIH with early onset and severe disease, while the HLA-DR4 serotype is more prevalent in Caucasians with late-onset disease. HLA-DR4 is also associated with higher rates of extrahepatic manifestations and improved steroid responsiveness.

The hallmark features of AIH are represented by its immunologic and autoimmunologic features in the setting of circulating autoantibodies and hyperglobulinemia. Despite the lack of convincing evidence establishing the role of these antibodies in the pathogenesis of AIH, 2 major forms of AIH have been proposed based on these immunologic features: type I AIH and type II AIH.

Type I AIH, also known as classic AIH, is characterized by antinuclear antibodies (ANA), antismooth muscle antibodies (ASMA), and IgG Actin (AAA). According to Frenzel et al., F-actin ELISA had superior sensitivity (100%) and similar specificity (98%) for diagnosis of AIH compared with the standard antismooth muscle antibody immunofluorescence testing [84]. Atypical p-ANCA, anti-SLA/LP (soluble liver antigen/liver pancreas antigens), and double-stranded DNA are some autoantibodies known to occur in type I AIH. Type II AIH is characterized by antibodies to liver/kidney microsomes (ALKM-1) and to liver cytosol antigen (ALC-1).

The mainstay of treatment for AIH is prednisone with or without azathioprine [85]. Various factors play a role in the relapse of AIH including lack of response to medication, intolerance to medication due to side effects, or disease recurrence after completion of course of treatment. A case

report described two patients with AIH refractory to standard treatment with the first patient requiring tacrolimus, mycophenolate mofetil, and budesonide to achieve remission. The second patient required rituximab as a replacement for sirolimus with an addition of mycophenolate mofetil and prednisone to achieve remission [86]. In a single-center study examining six patients with biopsy proven AIH refractory to prednisone and azathioprine, two infusions of rituximab 1000 mg two week apart led to biochemical improvement without serious side effects [87].

4.3. Risk of Malignancy. Among the various manifestations of AIH, hepatic and extrahepatic malignancies are present throughout the course of the disease in patients with AIH. Malignancies can arise secondary to the underlying disease process, appear independent of AIH, predispose to AIH, and occur due to prolonged immunomodulation therapy for AIH [88–94].

Hepatocellular carcinoma (HCC) is a known outcome in patients with AIH and cirrhosis with cirrhosis being a requirement for developing HCC [95–99]. Patients with AIH with the highest risk for HCC have certain defining features including cirrhosis for more than 10 years, portal hypertension and its sequelae, repetitive liver inflammation, and immunosuppressive therapy for more than 3 years [95, 96, 98–100]. In a study looking at the risk Yeoman et al. [97] established that HCC arises more frequently in AIH patients with cirrhosis at presentation (9.3% versus 3.4%, $P = 0.048$). Thus, cirrhosis in AIH appears to be a prerequisite for HCC development, which consequently arises at a rate of 1.1% per year and equally affects males and females. Another study reported an incidence rate of 0.3% cases per year of follow-up after the development of cirrhosis in AIH patients [101].

Hematogenous metastasis of hepatocellular carcinoma to the ascending colon in a patient with AIH has also been documented in a case report [102]. In another case report, gastric adenocarcinoma occurred after cadaveric liver transplantation in a patient with AIH; the exact role of the AIH in the development of the gastric cancer was not elucidated [103]. Just as AIH is suspected to contribute to the development of gastrointestinal cancers, it can also develop in the setting of a gastrointestinal malignancy. A case review asserted that AIH occurred de novo in 5 patients with hematologic malignancy and in 1 patient with colon cancer. The AIH occurred as an overlap with PSC and PBC in two of the cases. However, the review could not determine whether AIH developed due to the underlying disease itself or due to the cancer treatment [104]. We learn the following lessons:

(i) Immunogenic phenotypes, circulating autoantibodies, and clinical features have been used to characterize AIH due to its various manifestations.

(ii) The mainstay of treatment for AIH is prednisone with or without azathioprine.

(iii) HCC occurs more frequently in AIH patients with cirrhosis and may occur at a rate of 1.1% per year.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

References

[1] K. M. Boberg, R. W. Chapman, G. M. Hirschfield, A. W. Lohse, M. P. Manns, and E. Schrumpf, "Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue," *Journal of Hepatology*, vol. 54, no. 2, pp. 374–385, 2011.

[2] A. J. Czaja, "Diagnosis and management of the overlap syndromes of autoimmune hepatitis," *Canadian Journal of Gastroenterology*, vol. 27, no. 7, pp. 417–423, 2013.

[3] M. Kaya, P. Angulo, and K. D. Lindor, "Overlap of autoimmune hepatitis and primary sclerosing cholangitis: an evaluation of a modified scoring system," *Journal of Hepatology*, vol. 33, no. 4, pp. 537–542, 2000.

[4] E. M. M. Kuiper, P. E. Zondervan, and H. R. van Buuren, "Paris criteria are effective in diagnosis of primary biliary cirrhosis and autoimmune hepatitis overlap syndrome," *Clinical Gastroenterology and Hepatology*, vol. 8, no. 6, pp. 530–534, 2010.

[5] R. Chapman, J. Fevery, A. Kalloo et al., "Diagnosis and management of primary sclerosing cholangitis," *Hepatology*, vol. 51, no. 2, pp. 660–678, 2010.

[6] P. Angulo and K. D. Lindor, "Primary sclerosing cholangitis," *Hepatology*, vol. 30, no. 1, pp. 325–332, 1999.

[7] J.-N. Vauthey and L. H. Blumgart, "Recent advances in the management of cholangiocarcinomas," *Seminars in Liver Disease*, vol. 14, no. 2, pp. 109–114, 1994.

[8] T. Patel, "Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States," *Hepatology*, vol. 33, no. 6, pp. 1353–1357, 2001.

[9] Y. H. Shaib, J. A. Davila, K. McGlynn, and H. B. El-Serag, "Rising incidence of intrahepatic cholangiocarcinoma in the United States: a true increase?" *Journal of Hepatology*, vol. 40, no. 3, pp. 472–477, 2004.

[10] A. Bergquist, A. Ekbom, R. Olsson et al., "Hepatic and extrahepatic malignancies in primary sclerosing cholangitis," *Journal of Hepatology*, vol. 36, no. 3, pp. 321–327, 2002.

[11] G. Rudolph, D. Gotthardt, P. Kloeters-Plachky, D. Rost, H. Kulaksiz, and A. Stiehl, "In PSC with dominant bile duct stenosis, IBD is associated with an increase of carcinomas and reduced survival," *Journal of Hepatology*, vol. 53, no. 2, pp. 313–317, 2010.

[12] M. Jaiswal, N. F. LaRusso, L. J. Burgart, and G. J. Gores, "Inflammatory cytokines induce DNA damage and inhibit DNA repair in cholangiocarcinoma cells by a nitric oxide-dependent mechanism," *Cancer Research*, vol. 60, no. 1, pp. 184–190, 2000.

[13] W. R. Wu, X. D. Shi, R. Zhang et al., "Clinicopathological significance of aberrant Notch receptors in intrahepatic cholangiocarcinoma," *International Journal of Clinical and Experimental Pathology*, vol. 7, no. 6, pp. 3272–3279, 2014.

[14] M. El Khatib, P. Bozko, V. Palagani, N. P. Malek, L. Wilkens, and R. R. Plentz, "Activation of Notch signaling is required for cholangiocarcinoma progression and is enhanced by inactivation of p53 in vivo," *PloS one*, vol. 8, no. 10, Article ID e77433, 2013.

[15] R. V. Guest, L. Boulter, T. J. Kendall et al., "Cell lineage tracing reveals a biliary origin of intrahepatic cholangiocarcinoma," *Cancer Research*, vol. 74, no. 4, pp. 1005–1010, 2014.

[16] W.-R. Wu, R. Zhang, X.-D. Shi et al., "Notch1 is overexpressed in human intrahepatic cholangiocarcinoma and is associated with its proliferation, invasiveness and sensitivity to 5-fluorouracil in vitro," *Oncology Reports*, vol. 31, no. 6, pp. 2515–2524, 2014.

[17] M. T. Dill, L. Tornillo, T. Fritzius et al., "Constitutive Notch2 signaling induces hepatic tumors in mice," *Hepatology*, vol. 57, no. 4, pp. 1607–1619, 2013.

[18] E. Melum, T. H. Karlsen, E. Schrumpf et al., "Cholangiocarcinoma in primary sclerosing cholangitis is associated with NKG2D polymorphisms," *Hepatology*, vol. 47, no. 1, pp. 90–96, 2008.

[19] S. E. Kerr, E. G. Barr Fritcher, M. B. Campion et al., "Biliary dysplasia in primary sclerosing cholangitis harbors cytogenetic abnormalities similar to cholangiocarcinoma," *Human Pathology*, vol. 45, no. 9, pp. 1797–1804, 2014.

[20] N. Razumilava, G. J. Gores, and K. D. Lindor, "Cancer surveillance in patients with primary sclerosing cholangitis," *Hepatology*, vol. 54, no. 5, pp. 1842–1852, 2011.

[21] A. Serrablo and L. Tejedor, "Outcome of surgical resection in Klatskin tumors," *World Journal of Gastrointestinal Oncology*, vol. 5, no. 7, pp. 147–158, 2013.

[22] J. E. Eaton, J. A. Talwalkar, K. N. Lazaridis, G. J. Gores, and K. D. Lindor, "Pathogenesis of primary sclerosing cholangitis and advances in diagnosis and management," *Gastroenterology*, vol. 145, no. 3, pp. 521–536, 2013.

[23] G. Morris-Stiff, C. Bhati, S. Olliff et al., "Cholangiocarcinoma complicating primary sclerosing cholangitis: a 24-year experience," *Digestive Surgery*, vol. 25, no. 2, pp. 126–132, 2008.

[24] K. M. Boberg, A. Bergquist, S. Mitchell et al., "Cholangiocarcinoma in primary sclerosing cholangitis: risk factors and clinical presentation," *Scandinavian Journal of Gastroenterology*, vol. 37, no. 10, pp. 1205–1211, 2002.

[25] P. Manninen, A.-L. Karvonen, J. Laukkarinen, P. Aitola, H. Huhtala, and P. Collin, "Colorectal cancer and cholangiocarcinoma in patients with primary sclerosing cholangitis and inflammatory bowel disease," *Scandinavian Journal of Gastroenterology*, vol. 50, no. 4, pp. 423–428, 2015.

[26] A. Wee, J. Ludwig, R. J. Coffey Jr., N. F. LaRusso, and R. H. Wiesner, "Hepatobiliary carcinoma associated with primary sclerosing cholangitis and chronic ulcerative colitis," *Human Pathology*, vol. 16, no. 7, pp. 719–726, 1985.

[27] U. Broomé, R. Olsson, L. Lööf et al., "Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis," *Gut*, vol. 38, no. 4, pp. 610–615, 1996.

[28] N. Chalasani, A. Baluyut, A. Ismail et al., "Cholangiocarcinoma in patients with primary sclerosing cholangitis: a multicenter case-control study," *Hepatology*, vol. 31, no. 1, pp. 7–11, 2000.

[29] C. Levy, J. Lymp, P. Angulo, G. J. Gores, N. Larusso, and K. D. Lindor, "The value of serum CA 19-9 in predicting cholangiocarcinomas in patients with primary sclerosing cholangitis," *Digestive Diseases and Sciences*, vol. 50, no. 9, pp. 1734–1740, 2005.

[30] P. Charatcharoenwitthaya, F. B. Enders, K. C. Halling, and K. D. Lindor, "Utility of serum tumor markers, imaging, and biliary cytology for detecting cholangiocarcinoma in primary sclerosing cholangitis," *Hepatology*, vol. 48, no. 4, pp. 1106–1117, 2008.

[31] A. C. Berger, M. Garcia Jr., J. P. Hoffman et al., "Postresection CA 19-9 predicts overall survival in patients with pancreatic cancer treated with adjuvant chemoradiation: a prospective validation by RTOG 9704," *Journal of Clinical Oncology*, vol. 26, no. 36, pp. 5918–5922, 2008.

[32] Technology Assessment Committe, A. Barkun, J. Liu et al., "Update on endoscopic tissue sampling devices," *Gastrointestinal Endoscopy*, vol. 63, no. 6, pp. 741–745, 2006.

[33] K. Modha and U. Navaneethan, "Diagnosis and management of primary sclerosing cholangitis-perspectives from a therapeutic endoscopist," *World Journal of Hepatology*, vol. 7, no. 5, pp. 799–805, 2015.

[34] Y. Ishii, T. Sasaki, M. Serikawa et al., "Characteristic features of cholangiocarcinoma complicating primary sclerosing cholangitis," *Hepatogastroenterology*, vol. 61, no. 131, pp. 567–573, 2014.

[35] G. Trikudanathan, U. Navaneethan, B. Njei, J. J. Vargo, and M. A. Parsi, "Diagnostic yield of bile duct brushings for cholangiocarcinoma in primary sclerosing cholangitis: a systematic review and meta-analysis," *Gastrointestinal Endoscopy*, vol. 79, no. 5, pp. 783–789, 2014.

[36] U. Navaneethan, B. Njei, P. G. K. Venkatesh, J. J. Vargo, and M. A. Parsi, "Fluorescence in situ hybridization for diagnosis of cholangiocarcinoma in primary sclerosing cholangitis: a systematic review and meta-analysis," *Gastrointestinal Endoscopy*, vol. 79, no. 6, pp. 943–950.e3, 2014.

[37] A. Bergquist, B. Tribukait, H. Glaumann, and U. Broomé, "Can DNA cytometry be used for evaluation of malignancy and premalignancy in bile duct strictures in primary sclerosing cholangitis?" *Journal of Hepatology*, vol. 33, no. 6, pp. 873–877, 2000.

[38] J. E. Eaton, E. G. Barr Fritcher, G. J. Gores et al., "Biliary multifocal chromosomal polysomy and cholangiocarcinoma in primary sclerosing cholangitis," *The American Journal of Gastroenterology*, vol. 110, no. 2, pp. 299–309, 2015.

[39] K. Andresen, K. M. Boberg, H. M. Vedeld et al., "Four DNA methylation biomarkers in biliary brush samples accurately identify the presence of cholangiocarcinoma," *Hepatology*, vol. 61, no. 5, pp. 1651–1659, 2015.

[40] U. Navaneethan, M. A. Parsi, D. Lourdusamy et al., "Volatile organic compounds in urine for noninvasive diagnosis of malignant biliary strictures: a pilot study," *Digestive Diseases and Sciences*, vol. 60, no. 7, pp. 2150–2157, 2015.

[41] T. Voigtländer, S. K. Gupta, S. Thum et al., "MicroRNAs in serum and bile of patients with primary sclerosing cholangitis and/or cholangiocarcinoma," *PLOS ONE*, vol. 10, no. 10, article e0139305, 2015.

[42] T. O. Lankisch, J. Metzger, A. A. Negm et al., "Bile proteomic profiles differentiate cholangiocarcinoma from primary sclerosing cholangitis and choledocholithiasis," *Hepatology*, vol. 53, no. 3, pp. 875–884, 2011.

[43] M.-M. Xu and A. Sethi, "Diagnosing biliary malignancy," *Gastrointestinal Endoscopy Clinics of North America*, vol. 25, no. 4, pp. 677–690, 2015.

[44] Y. K. Chen, M. A. Parsi, K. F. Binmoeller et al., "Single-operator cholangioscopy in patients requiring evaluation of bile duct disease or therapy of biliary stones (with videos)," *Gastrointestinal Endoscopy*, vol. 74, no. 4, pp. 805–814, 2011.

[45] E. Kalaitzakis, G. J. Webster, K. W. Oppong et al., "Diagnostic and therapeutic utility of single-operator peroral cholangioscopy for indeterminate biliary lesions and bile duct stones," *European Journal of Gastroenterology and Hepatology*, vol. 24, no. 6, pp. 656–664, 2012.

[46] R. J. Shah, "Cholangiocarcionoma and primary sclerosing cholangitis: the answer lies within," *Gastrointestinal Endoscopy*, vol. 79, no. 5, pp. 780–782, 2014.

[47] E. Kalaitzakis, R. Sturgess, H. Kaltsidis et al., "Diagnostic utility of single-user peroral cholangioscopy in sclerosing cholangitis," *Scandinavian Journal of Gastroenterology*, vol. 49, no. 10, pp. 1237–1244, 2014.

[48] N. Azeem, C. J. Gostout, M. Knipschield, and T. H. Baron, "Cholangioscopy with narrow-band imaging in patients with primary sclerosing cholangitis undergoing ERCP," *Gastrointestinal Endoscopy*, vol. 79, no. 5, pp. 773–779e2, 2014.

[49] M. Heif, R. D. Yen, and R. J. Shah, "ERCP with probe-based confocal laser endomicroscopy for the evaluation of dominant biliary stenoses in primary sclerosing cholangitis patients," *Digestive Diseases and Sciences*, vol. 58, no. 7, pp. 2068–2074, 2013.

[50] A. Meining, R. J. Shah, A. Slivka et al., "Classification of probe-based confocal laser endomicroscopy findings in pancreaticobiliary strictures," *Endoscopy*, vol. 44, no. 3, pp. 251–257, 2012.

[51] A. Meining, Y. K. Chen, D. Pleskow et al., "Direct visualization of indeterminate pancreaticobiliary strictures with probe-based confocal laser endomicroscopy: a multicenter experience," *Gastrointestinal Endoscopy*, vol. 74, no. 5, pp. 961–968, 2011.

[52] R. L. Siegel, K. D. Miller, and A. Jemal, "Cancer statistics, 2016," *CA: A Cancer Journal for Clinicians*, vol. 66, no. 1, pp. 7–30, 2016.

[53] U. Broomé, R. Löfberg, B. Veress, and L. S. Eriksson, "Primary sclerosing cholangitis and ulcerative colitis: evidence for increased neoplastic potential," *Hepatology*, vol. 22, no. 5, pp. 1404–1408, 1995.

[54] A. N. Ananthakrishnan, A. Cagan, V. S. Gainer et al., "Mortality and extraintestinal cancers in patients with primary sclerosing cholangitis and inflammatory bowel disease," *Journal of Crohn's and Colitis*, vol. 8, no. 9, pp. 956–963, 2014.

[55] R. M. Soetikno, O. S. Lin, P. A. Heidenreich, H. S. Young, and M. O. Blackstone, "Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis: a meta-analysis," *Gastrointestinal Endoscopy*, vol. 56, no. 1, pp. 48–54, 2002.

[56] E. V. Loftus Jr., G. C. Harewood, C. G. Loftus et al., "PSC-IBD: a unique form of inflammatory bowel disease associated with primary sclerosing cholangitis," *Gut*, vol. 54, no. 1, pp. 91–96, 2005.

[57] H. Jayaram, J. Satsangi, and R. W. Chapman, "Increased colorectal neoplasia in chronic ulcerative colitis complicated by primary sclerosing cholangitis: fact or fiction?" *Gut*, vol. 48, no. 3, pp. 430–434, 2001.

[58] F. P. Vleggaar, M. W. M. D. Lutgens, and M. M. H. Claessen, "Review article: the relevance of surveillance endoscopy in long-lasting inflammatory bowel disease," *Alimentary Pharmacology and Therapeutics*, vol. 26, supplement 2, pp. 47–52, 2007.

[59] T. Kitiyakara and R. W. Chapman, "Chemoprevention and screening in primary sclerosing cholangitis," *Postgraduate Medical Journal*, vol. 84, no. 991, pp. 228–237, 2008.

[60] G. G. Kaplan, S. J. Heitman, R. J. Hilsden et al., "Population-based analysis of practices and costs of surveillance for colonic dysplasia in patients with primary sclerosing cholangitis and colitis," *Inflammatory Bowel Diseases*, vol. 13, no. 11, pp. 1401–1407, 2007.

[61] M. T. Carriaga and D. E. Henson, "Liver, gallbladder, extrahepatic bile ducts, and pancreas," *Cancer*, vol. 75, supplement 1, pp. 171–190, 1995.

[62] D. C. Buckles, K. D. Lindor, N. F. LaRusso, L. M. Petrovic, and G. J. Gores, "In primary sclerosing cholangitis, gallbladder polyps are frequently malignant," *The American Journal of Gastroenterology*, vol. 97, no. 5, pp. 1138–1142, 2002.

[63] R. Zenouzi, T. J. Weismüller, P. Hübener et al., "Low risk of hepatocellular carcinoma in patients with primary sclerosing cholangitis with cirrhosis," *Clinical Gastroenterology and Hepatology*, vol. 12, no. 10, pp. 1733–1738, 2014.

[64] M. I. Prince, A. Chetwynd, P. Diggle, M. Jarner, J. V. Metcalf, and O. F. W. James, "The geographical distribution of primary biliary cirrhosis in a well-defined cohort," *Hepatology*, vol. 34, no. 6, pp. 1083–1088, 2001.

[65] R. J. Q. McNally, P. W. James, S. Ducker, P. D. Norman, and O. F. W. James, "No rise in incidence but geographical heterogeneity in the occurrence of primary biliary cirrhosis in north east england," *American Journal of Epidemiology*, vol. 179, no. 4, pp. 492–498, 2014.

[66] C. R. Muirhead, O. F. W. James, S. J. Ducker, and R. J. Q. McNally, "Does primary biliary cirrhosis cluster in time?" *Spatial and Spatio-temporal Epidemiology*, vol. 14-15, pp. 1–8, 2015.

[67] A. F. Gulamhusein, B. D. Juran, and K. N. Lazaridis, "Genome-wide association studies in primary biliary cirrhosis," *Seminars in Liver Disease*, vol. 35, no. 4, pp. 392–401, 2015.

[68] J. Underbill, P. Donaldson, G. Bray, D. Doherty, B. Portmann, and R. Williams, "Susceptibility to primary biliary cirrhosis is associated with the HLA-DR8-DQB1 *0402 haplotype," *Hepatology*, vol. 16, no. 6, pp. 1404–1408, 1992.

[69] J. A. Underhill, P. T. Donaldson, D. G. Doherty, K. Manabe, and R. Williams, "HLA DPB polymorphism in primary sclerosing cholangitis and primary biliary cirrhosis," *Hepatology*, vol. 21, no. 4, pp. 959–962, 1995.

[70] L. Wang, Y. Sun, Z. Zhang et al., "$CXCR5^+$ $CD4^+$ T follicular helper cells participate in the pathogenesis of primary biliary cirrhosis," *Hepatology*, vol. 61, no. 2, pp. 627–638, 2015.

[71] F. Limongi, "Th1 cytokines and chemokines in primary biliary cirrhosis," *Clinical Therapeutics*, vol. 166, no. 2, pp. e122–e125, 2015.

[72] V. Thomas, B. Chipchase, L. Rippon, and P. McArdle, "The application of mental health legislation in younger children," *BJPsych Bulletin*, vol. 39, no. 6, pp. 302–304, 2015.

[73] M. Deutsch, G. V. Papatheodoridis, A. Tzakou, and S. J. Hadziyannis, "Risk of hepatocellular carcinoma and extrahepatic malignancies in primary biliary cirrhosis," *European Journal of Gastroenterology and Hepatology*, vol. 20, no. 1, pp. 5–9, 2008.

[74] A. Cavazza, L. Caballerí, A. Floreani et al., "Incidence, risk factors, and survival of hepatocellular carcinoma in primary biliary cirrhosis: comparative analysis from two centers," *Hepatology*, vol. 50, no. 4, pp. 1162–1168, 2009.

[75] S. Nair, A. Mason, J. Eason, G. Loss, and R. P. Perrillo, "Is obesity an independent risk factor for hepatocellular carcinoma in cirrhosis?" *Hepatology*, vol. 36, no. 1, pp. 150–155, 2002.

[76] K. Boonstra, R. Bokelaar, P. H. Stadhouders et al., "Increased cancer risk in a large population-based cohort of patients with primary biliary cirrhosis: follow-up for up to 36 years," *Hepatology International*, vol. 8, no. 2, pp. 266–274, 2014.

[77] Y. Liang, Z. Yang, and R. Zhong, "Primary biliary cirrhosis and cancer risk: a systematic review and meta-analysis," *Hepatology*, vol. 56, no. 4, pp. 1409–1417, 2012.

[78] P. J. Trivedi, W. J. Lammers, H. R. van Buuren et al., "Stratification of hepatocellular carcinoma risk in primary biliary

cirrhosis: a multicentre international study," *Gut*, vol. 65, no. 2, pp. 321–329, 2016.

[79] B. M. Goudie, A. D. Burt, P. Boyle et al., "Breast cancer in women with primary biliary cirrhosis," *British Medical Journal*, vol. 291, no. 6509, pp. 1597–1598, 1985.

[80] A. M. Wolke, F. Schaffner, B. Kapelman, and H. S. Sacks, "Malignancy in primary biliary cirrhosis. High incidence of breast cancer in affected women," *The American Journal of Medicine*, vol. 76, no. 6, pp. 1075–1078, 1984.

[81] A. Floreani, M. R. Biagini, M. Chiaramonte, S. Milani, C. Surrenti, and R. Naccarato, "Incidence of hepatic and extrahepatic malignancies in primary biliary cirrhosis (PBC)," *Italian Journal of Gastroenterology*, vol. 25, no. 9, pp. 473–476, 1993.

[82] L. Lööf, H.-O. Adami, P. Sparén et al., "Cancer risk in primary biliary cirrhosis: a population-based study from Sweden," *Hepatology*, vol. 20, no. 1, part 1, pp. 101–104, 1994.

[83] E. Kokue and Y. Takahashi, "Protective effect of sodium polyacrylate on induced duodenal ulceration in guinea pigs," *Japanese Journal of Pharmacology*, vol. 26, no. 6, pp. 760–762, 1976.

[84] C. Frenzel, J. Herkel, S. Lüth, P. R. Galle, C. Schramm, and A. W. Lohse, "Evaluation of F-actin ELISA for the diagnosis of autoimmune hepatitis," *The American Journal of Gastroenterology*, vol. 101, no. 12, pp. 2731–2736, 2006.

[85] M. P. Manns, A. J. Czaja, J. D. Gorham et al., "Diagnosis and management of autoimmune hepatitis," *Hepatology*, vol. 51, no. 6, pp. 2193–2213, 2010.

[86] J. N. Rubin and H. S. Te, "Refractory autoimmune hepatitis: beyond standard therapy," *Digestive Diseases and Sciences*, vol. 61, no. 6, pp. 1757–1762, 2016.

[87] K. W. Burak, M. G. Swain, T. Santodomingo-Garzon et al., "Rituximab for the treatment of patients with autoimmune hepatitis who are refractory or intolerant to standard therapy," *Canadian Journal of Gastroenterology and Hepatology*, vol. 27, no. 5, pp. 273–280, 2013.

[88] M. Werner, S. Almer, H. Prytz et al., "Hepatic and extrahepatic malignancies in autoimmune hepatitis. A long-term follow-up in 473 Swedish patients," *Journal of Hepatology*, vol. 50, no. 2, pp. 388–393, 2009.

[89] K. K. Wang, A. J. Czaja, S. J. Beaver, and V. L. W. Go, "Extrahepatic malignancy following long-term immunosuppressive therapy of severe hepatitis B surface antigen-negative chronic active hepatitis," *Hepatology*, vol. 10, no. 1, pp. 39–43, 1989.

[90] J. Leung, L. Dowling, I. Obadan et al., "Risk of non-melanoma skin cancer in autoimmune hepatitis," *Digestive Diseases and Sciences*, vol. 55, no. 11, pp. 3218–3223, 2010.

[91] L. Váróczy, L. Gergely, M. Zeher, G. Szegedi, and Á. Illés, "Malignant lymphoma-associated autoimmune diseases—a descriptive epidemiological study," *Rheumatology International*, vol. 22, no. 6, pp. 233–237, 2002.

[92] C. E. M. De Block, I. H. De Leeuw, P. A. Pelckmans et al., "Autoimmune hepatitis, autoimmune gastritis, and gastric carcinoid in a type 1 diabetic patient: a case report," *Journal of Diabetes and its Complications*, vol. 14, no. 2, pp. 116–120, 2000.

[93] H. Kondo, J. Watanabe, and H. Iwasaki, "T-large granular lymphocyte leukemia accompanied by an increase of natural killer cells (CD3-) and associated with ulcerative colitis and autoimmune hepatitis," *Leukemia and Lymphoma*, vol. 41, no. 1-2, pp. 207–212, 2001.

[94] C. G. Begley, I. R. Mackay, and P. S. Bhathal, "Another immune-mediated disease associated with hairy cell leukemia: chronic active hepatitis," *Acta Haematologica*, vol. 73, no. 2, pp. 104–105, 1985.

[95] K. K. Wang and A. J. Czaja, "Hepatocellular carcinoma in corticosteroid-treated severe autoimmune chronic active hepatitis," *Hepatology*, vol. 8, no. 6, pp. 1679–1683, 1988.

[96] A. J. Montano-Loza, H. A. Carpenter, and A. J. Czaja, "Predictive factors for hepatocellular carcinoma in type 1 autoimmune hepatitis," *The American Journal of Gastroenterology*, vol. 103, no. 8, pp. 1944–1951, 2008.

[97] A. D. Yeoman, T. Al-Chalabi, J. B. Karani et al., "Evaluation of risk factors in the development of hepatocellular carcinoma in autoimmune hepatitis: implications for follow-up and screening," *Hepatology*, vol. 48, no. 3, pp. 863–870, 2008.

[98] S. Z. Park, D. M. Nagorney, and A. J. Czaja, "Hepatocellular carcinoma in autoimmune hepatitis," *Digestive Diseases and Sciences*, vol. 45, no. 10, pp. 1944–1948, 2000.

[99] R. J. Wong, R. Gish, T. Frederick, N. Bzowej, and C. Frenette, "Development of hepatocellular carcinoma in autoimmune hepatitis patients: a case series," *Digestive Diseases and Sciences*, vol. 56, no. 2, pp. 578–585, 2011.

[100] Y. Miyake, Y. Iwasaki, R. Terada et al., "Persistent elevation of serum alanine aminotransferase levels leads to poor survival and hepatocellular carcinoma development in type 1 autoimmune hepatitis," *Alimentary Pharmacology and Therapeutics*, vol. 24, no. 8, pp. 1197–1205, 2006.

[101] A. Danielsson Borssén, S. Almer, H. Prytz et al., "Hepatocellular and extrahepatic cancer in patients with autoimmune hepatitis—a long-term follow-up study in 634 Swedish patients," *Scandinavian Journal of Gastroenterology*, vol. 50, no. 2, pp. 217–223, 2015.

[102] N. Tapuria, C. K. Sinha, N. G. Michael, and P. W. Fisher, "Haematogenous metastasis to ascending colon in a patient with hepatocellular carcinoma and autoimmune hepatitis," *European Journal of Gastroenterology and Hepatology*, vol. 19, no. 7, pp. 607–609, 2007.

[103] Ç. Arslan, S. Kiliçkap, and Ş. Yalçin, "Gastric cancer after cadaveric liver transplantation in a patient with autoimmune hepatitis: a case report and review of the literature," *Turkish Journal of Gastroenterology*, vol. 22, no. 1, pp. 73–76, 2011.

[104] P. Milkiewicz, D. Mutimer, S. G. Hubscher, and E. Elias, "Autoimmune liver disease in patients with neoplastic diseases," *European Journal of Gastroenterology and Hepatology*, vol. 11, no. 5, pp. 569–573, 1999.

Hindawi Publishing Corporation
Gastroenterology Research and Practice
Volume 2016, Article ID 5249152, 7 pages
http://dx.doi.org/10.1155/2016/5249152

Review Article

Advances in Therapeutic Cholangioscopy

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Received 22 January 2016; Revised 11 April 2016; Accepted 18 April 2016

Academic Editor: Sooraj Tejaswi

Nowadays, cholangioscopy is an established modality in diagnostic and treatment of pancreaticobiliary diseases. The more widespread use and the recent development of new technologies and accessories had renewed the interest of endoscopic visualization of the biliary tract, increasing the range of indications and therapeutic procedures, such as diagnostic of indeterminate biliary strictures, lithotripsy of difficult bile duct stones, ablative techniques for intraductal malignancies, removal of foreign bodies and gallbladder drainage. These endoscopic interventions will probably be the last frontier in the near future. This paper presents the new advances in therapeutic cholangioscopy, focusing on the current clinical applications and on research areas.

1. Introduction

In recent decades, endoscopic retrograde cholangiopancreatography (ERCP) had been the primary tool in the endoscopic treatment of biliary tract diseases, with success rates above 90% [1–3]. Nevertheless, some situations remain challenging, with difficult diagnosis and treatment, as indeterminate biliary strictures and stones of difficult removal.

In this context, cholangioscopy was introduced in order to improve diagnostic and therapy of biliary diseases, allowing direct visualization of the biliary system and also performance of therapeutic interventions [4].

Endoscopic evaluation of the biliary tree is not a recent procedure, as some may believe. The first optical choledocoscope was developed in 1941 and the peroral approach in 1976, initially through a prototype that was thin enough to be inserted through the working channel of the duodenoscope [5, 6]. This system was known as "mother-baby scope," requiring two endoscopists for its management. This first prototype had a fiber-optic camera, low quality, and neither working channels nor irrigation and was without tip deflection. Its use remained limited, mainly due to the high cost, fragility, and requirement of two experienced endoscopists. Despite these limitations, it was possible to prove that the peroral cholangioscopy was feasible [7–9].

From the mid-80s, the second generation of cholangioscopes was developed with larger diameters, tip deflections, and working channels, allowing the introduction of instruments and irrigation [6]. Also, with the advancement of technology, there was improvement of the image allowing proper evaluation of the biliary tract mucosa and lumen.

In 2007, the first cholangioscopy platform was introduced with a unit of single-operator (SpyGlass®), making the procedure more feasible and effective, enabling accurate biopsies and lithotripsy under direct visualization. Consequently, for its numerous advantages, the use of SpyGlass gained popularity, with great advantages in everyday practice [2]. In 2014, the second generation was introduced, with higher quality image (SpyGlass DS®), and also important improvements as ergonomics, stability, accessory exposure, and larger working channel (Figure 1).

Single-operator system with "ultraslim" endoscopes with an external diameter ranging from 5 to 6 mm can also be used. Because of its diameter, the presence of dilated biliary duct and previously sphincterotomy is necessary. The major advantage is the superior digital image quality [2, 3], especially desirable in diagnostic procedures.

The recent development of new technologies, including high-definition images and the incorporation of optical chromoendoscopy (NBI), has renewed interest in endoscopic

Table 1: Cholangioscopy modalities.

Type		Advantages	Disadvantages	Endoscope diameter	Work channel
Dual-operator	"Mother-baby"	It was the first optical choledoscope developed	Necessary of two experienced endoscopists, low image quality, difficulty in handling, fragility, limited capacity of suction and irrigation, and small diameter of working channel, limiting therapeutic procedures	"Mother": 12.6 mm "Baby": 2.8–3.4 mm	0.8–1.2 mm
	Karl Storz (short-access-mother-baby)	More maneuverability, short size with less fragility, larger work channel	Necessity of two experienced endoscopists, only two-way deflected steering tip	"Mother": 12.6 mm "Baby": 3.4 mm	1.5 mm
Single-operator	Boston Scientific (SpyGlass)	Only one endoscopist, four-direction tip deflection	High cost, work channel diameter	3.3 mm	1.2 mm
	Ultra-slim endoscopes (direct peroral cholangioscopy) (Olympus, Pentax, Fujinon)	Superior video image quality with narrow band imaging capability, larger size of the work channel	High cost, can only be performed in dilated bile ducts, difficulty of insertion into the bile duct, lack of stability	5-6 mm	2.0–2.2 mm

Figure 1: SpyGlass DS: cholangioscopy single-operator platform.

visualization of the biliary tree and led to more widespread use of cholangioscopy [4, 10–15]. Cholangioscopy modalities are summarized in Table 1.

It is a fact that most of cholangioscopy indications are to evaluate indeterminate biliary strictures. In the present paper, we have focused on the advances of therapeutic cholangioscopy, highlighting the large potential of this issue in our clinical practice. Diagnostic applications are not on the scope of this issue. Currently, the established indication of cholangioscopy in therapeutic field is to treat difficult biliary stones, when associated with electrohydraulic lithotripsy (EHL) or laser lithotripsy (LL). Nevertheless, the indications continued to expand and several applications have been described, such as treatment of biliary strictures, lithotripsy of pancreatic duct stones, tumor ablation, gallbladder and biliary drainage, guidewire placement, foreign body removal, and the diagnosis and treatment of hemobilia, as discussed below.

2. Lithotripsy for Difficult Biliary Stones

Approximately 10–15% of stones cannot be extracted by ERCP conventional methods under certain circumstances, needing additional or other therapeutic modalities [15, 16]. Furthermore, it has been shown that previous ERCPs failed to correctly identify choledocholithiasis in 8%–16% of cases [14].

The definition of difficult bile duct stones is complex and involves many factors such as size (usually stones larger than 15 mm), disproportion of the stone with the distal common bile duct, postoperative anatomical changes, stenosis, presence of multiple and barrel-shaped stones, and inaccessible locations (intrahepatic stones, the Mirizzi syndrome) [11, 13, 15].

Lithotripsy guided by cholangioscopy allows stone fragmentation through electrohydraulic waves (EHL) (Figure 2) or laser (LL), facilitating the subsequent removal with conventional accessories. Several studies report success rates of 80–90% and these results are frequently achieved in just one session [2, 9, 11–14]. Thus, lithotripsy under direct visualization is safer because it helps prevent bile duct injury and reduces the need for mechanical lithotripsy [4, 15].

EHL is performed through a 1.9 Fr nitinol fiber containing two electrodes in its tip. High amplitude hydraulic pressure waves are created, requiring immersion in saline solution. A generator produces a series of electrical pulses of high voltage at a frequency of 1 to 20 seconds, with a power of 50 to 100 watts.

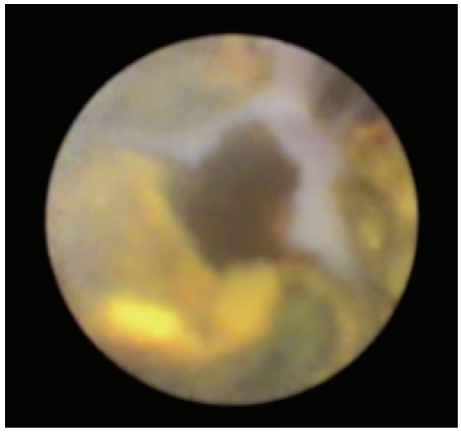

Figure 2: Broken bile duct large stone after EHL session.

LL is performed using a pulse holmium YAG or aluminum transmitted through a flexible quartz fiber. The application of repeated pulses of energy leads to accumulation of gaseous ions and free electrons, inducing a wave of mechanical shock and causing stone fragmentation. Irrigation is necessary to allow laser propagation and to ensure adequate clearance from the duct during the procedure.

The effectiveness of the electrohydraulic and laser lithotripsy is similar in terms of stone fragmentation rates, but LL seems to be more expensive and requires more time [4, 15].

In case of intrahepatic stones, the thinner LL probe is generally preferred to the EHL probe, whereas the EHL is the most widely used technique, particularly with the SpyGlass system, because of the dedicated irrigation channel providing the flowing water that is required to perform the EHL [14]. Percutaneous transhepatic cholangioscopy-(PTCS-) EHL/laser lithotripsy is probably the only alternative to surgery for removal of intrahepatic stones [15, 17, 18].

Regarding the Mirizzi syndrome, the conventional management has been surgical and endoscopic treatment is still controversial, except to relieve a bile duct obstruction, with limited data regarding the effectiveness or complication rate of this approach [19–21]. Binmoeller et al. [22] demonstrated 100% success when treating 14 patients with Mirizzi's syndrome and Tsuyuguchi et al. [21] successfully treated 23 of 25 patients (92%), concluding that endoscopic treatment of patients with the Mirizzi syndrome is effective and less invasive compared with surgery in those with type II syndrome. In patients with type I, the stones may not be accessible to the cholangioscope, and surgery may be preferable.

3. Ablation Techniques

The ablative therapies for intraductal cancer guided by cholangioscopy are increasingly being applied and aim to improve cholestasis, survival, and quality of life [15]. These techniques include various forms and can be performed directly (e.g., brachytherapy and radiofrequency ablation) or indirectly (e.g., photodynamic therapy).

3.1. Photodynamic Therapy (PDT). PDT has become an ascending mode for the treatment of unresectable cholangiocarcinoma and involves intravenous administration of a photosensitizer which is accumulated preferentially in tumor cells, followed by exposure of the tissue to the photocuring light, by generating cytotoxic reaction and subsequently ischemia, necrosis, and apoptosis of tumor cells. In many studies, patients undergoing PDT showed an increased survival rate compared with conventional stenting alone [23, 24]. Cholangioscopy may be useful for determining the extent of the spread of bile duct tumors and the appropriate location of the diffuser for light activation as well as for evaluating the clinical response to PDT.

Ortner et al. [24] performed a randomized control trial comparing stenting + PDT with stenting alone in 39 patients with histologically confirmed cholangiocarcinoma. PDT resulted in prolongation of survival ($P < 0.0001$). It also improved biliary drainage and quality of life. This study was terminated prematurely because PDT proved to be so superior to simple stenting treatment that further randomization was deemed unethical. Other studies also proved the advantages of PDT [25].

3.2. Radiofrequency Ablation (RFA). RFA is the most promising endoscopic ablative technique nowadays due to its potential benefits, including reduced mortality and morbidity [23]. It is performed through catheters that induce thermal damage to the tissue by electromagnetic energy. Direct cholangioscopy can be useful in confirming a successful response to therapy.

Several authors [23, 26] described the feasibility and effectiveness of this technique; however, more randomized controlled trials are needed to compare its benefit against other treatments.

3.3. Brachytherapy. Intraductal brachytherapy (IB) is performed using a catheter positioned directly into the biliary stricture area, to apply iridium-192 isotopes. Radiation doses may vary from 10.4 to 20 Gy. It has the advantage of affecting only the desired location and a small area around, preventing tumor growth and avoiding unnecessary irradiation. It can be performed either endoscopically or percutaneously [23].

The effectiveness of this technique remains controversial in literature. Montemaggi et al. [27] described 12 patients submitted to intraluminal brachytherapy (eight on the bile duct and four on pancreatic duct). The results suggested that the addition of IB after biliary drainage prolongs survival. However, complications as cholangitis and gastrointestinal toxicities occurred in nine patients. Deodato et al. [28] evaluated long-term effects of IB, with clinical response rate of 28.6%, complete response in 9%, and median survival of 23 months. In conclusion, the role of IB in biliary cancer may be further analyzed in larger clinical trials.

4. Foreign Body Removal

Cholangioscopy-guided foreign body removal has been described in some case series.

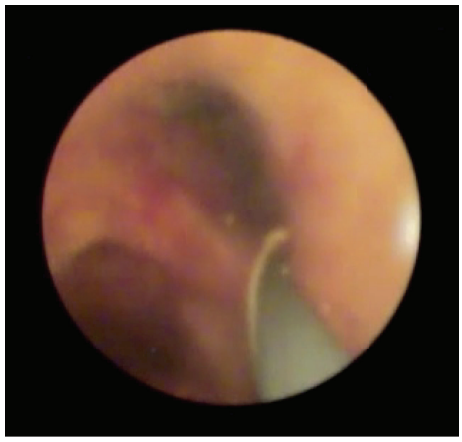

Figure 3: Direct view cholangioscopy enabling the adequate placement of guidewire through a biliary stricture.

Hasan et al. [29], using the new digital SpyGlass cholangioscope, performed direct endoscopic evaluation of a benign biliary stricture and identified a staple protruding through the biliary mucosa, which could have been a nidus for stricture formation. The staple was then removed by using SpyBite® biopsy forceps.

Basket impaction of a bile duct stone is a well-known problem occurring during endoscopic transpapillary lithotripsy. Generally, it is resolved by a transoral endotripter. However, even if the endotripter is used, sometimes it failed when the wires break because of the hardness of the stone. Wong et al. and Tsuchiya et al. [30, 31] described a successful removal of basket-impacted stone by use of transpapillary cholangioscopic electrohydraulic lithotripsy (EHL) and laser.

Cholangioscopy can be a useful tool to remove occluded or migrated biliary stents that cannot be removed with conventional techniques. Sanaka et al. and Sejpal et al. [32, 33] performed a retrieval of migrated biliary stent with direct peroral cholangioscopy, one by grasping with a thin snare and the other by cannulating with a guidewire and a stent retriever. Ikeura et al. [34] described a reintervention for an occluded metal stent under the guidance of peroral direct cholangioscopy by using an ultraslim enteroscope.

5. Guidewire Placement

Occasionally, guidewire placement can be a challenge, requiring more invasive procedures, such as percutaneous access or surgery. Using a cholangioscope, under direct visualization, the guidewire can be easily manipulated and placed in the desired location [35] (Figure 3).

6. Gallbladder Drainage

The gold standard treatment for acute cholecystitis is surgery. Nevertheless, some patients are not amenable due to significant comorbidities. In this case, percutaneous cholecystostomy is an alternative to surgery. Although a simple procedure, there are several complications, rating from 9 to 27% and including hemobilia, hematoma, and bile leak. When this technique is contraindicated or anatomically inaccessible, endoscopic-guided drainage can be used [36–38].

Cholangioscopy has significant advantages over ERCP in allowing direct visualization of the bile duct and obtaining targeted cystic duct cannulation. Itoi et al. [39] published a systematic review that revealed that endoscopic gallbladder stenting had a technical success rate of 96% and a clinical success rate of 88% which compared favorably with percutaneous transhepatic gallbladder drainage (98% and 90%, resp.). More investigations that compare cholangioscopy-assisted procedures and those without cholangioscopy are needed to evaluate the efficacy of this technique.

Shin et al. [36] reported 8 cases of SpyGlass-assisted gallbladder drainage, with a technical and clinical success rate of 88% and 75%, respectively. Complications such as pancreatitis, bleeding, and perforation did not occur in any patient.

7. Hemostasia

There are few cases reporting cholangioscopy diagnostic and therapeutic of bleeding lesions in the biliary mucosa [40–42]. Komaki et al. [40] reported a case of argon plasma coagulation under direct peroral cholangioscopy in a patient with hereditary hemorrhagic telangiectasia and repeated hemobilia.

8. Postliver Transplant Biliary Stricture

Cholangioscopy has been very useful in the evaluation and treatment of biliary complications after liver surgery. Direct visualization of the bile ducts may be a useful adjunct to endoscopic retrograde cholangiopancreatography (ERCP) for the evaluation of biliary strictures [43, 44]. Cholangioscopy increases the ability to evaluate mucosal changes and presence of fibrosis and provides direct intraductal therapies.

The safety and feasibility of single-operator cholangioscopy-guided steroids injection has been demonstrated by Franzini et al. [45] in a patient with refractory anastomotic biliary stricture after liver transplant. The patient underwent two sessions of cholangioscopy-guided steroid injection immediately after biliary balloon dilation, with 40 mg of triamcinolone acetate injected per session (Figure 4). It was the first report of a benign biliary stricture (BBS) treated by extreme balloon dilation combined with cholangioscopy-guided steroid injection. Randomized controlled trials could confirm if this technique has the potential to become a standard treatment for refractory BBS.

Severe anastomotic stricture after living donor transplant is a challenge to endoscopic treatment, mainly due to the inability to advance the guidewire through the stenotic area. In these cases, cholangioscopy commonly enables successful guidewire placement as described in report cases [46–48].

Another interesting field of application cholangioscopy is the evaluation and treatment of biliary cast syndrome,

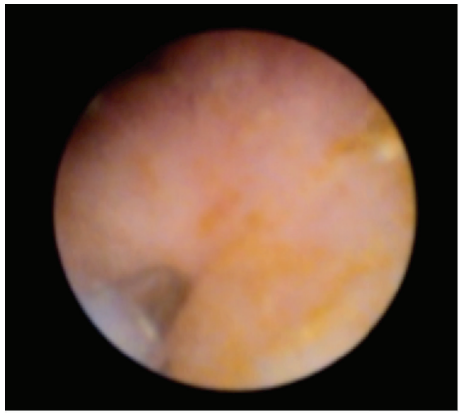

Figure 4: Cholangioscopy-guided steroid injection.

a condition usually associated with biliary strictures and hepatic ischemia after liver transplant. Navaneethan et al. [49] reported a complete cholangioscopy removal of biliary cast using single-operator cholangioscopy in a single sitting.

Biopsies samples of the stricture site under direct visualization with the use of SpyBite forceps have been done successfully after evaluation of mucosal abnormalities [50, 51]. Balderramo et al. [50] described 2 different cholangioscopic anastomotic stricture patterns, based on direct view. That may help to predict responses to endoscopic therapy. Pattern A was defined as mild erythema, and had better response to endoscopic treatment than pattern B characterized by edema, ulceration and sloughing. The histological findings showed nonspecific inflammatory changes.

9. Primary Sclerosing Cholangitis

The role of cholangioscopy in Primary Sclerosing Cholangitis (PSC) is to perform imaging of the biliary tract aiming at studying biliary strictures, characterizing dominant bile duct stenosis, enabling target biopsies of dysplastic lesions, and management of biliary stones.

Awadallah et al. [52] evaluated dominant strictures and cholangioscopy-directed stone therapy in PSC with demonstrable clinical benefits. Some other studies [53–57] have shown the effectiveness and usefulness of cholangioscopy in PSC, improving the detection of dysplastic lesions and allowing directed biopsies.

10. Resections

Although there are no published data on the therapeutic applications of cholangioscopy for the resection of a biliary lesion, a biliary polypoid lesion could be removed using a 5-F snare [14].

11. Conclusion

New therapeutic applications for cholangioscopy are emerging in the last years. Diffusion of single-operator concept, addition of digital imaging, and increase of availability of cholangioscopes surely played an important role.

The development of new accessories, as well as controlled trials evidence, will contribute in the near future to expand the indications of interventional cholangioscopy.

Competing Interests

Eduardo G. H. de Moura is a consultant for Boston Scientific. All other authors declare that there are no competing interests regarding the publication of this paper.

References

[1] M. A. Parsi, "Direct peroral cholangioscopy," *World Journal of Gastrointestinal Endoscopy*, vol. 6, no. 1, pp. 1–5, 2014.

[2] J. B. Williamson and P. V. Draganov, "The usefulness of spyglass™ choledochoscopy in the diagnosis and treatment of biliary disorders," *Current Gastroenterology Reports*, vol. 14, no. 6, pp. 534–541, 2012.

[3] M. A. Parsi, "Peroral cholangioscopy in the new millennium," *World Journal of Gastroenterology*, vol. 17, no. 1, pp. 1–6, 2011.

[4] J. H. Moon, G. Terheggen, H. J. Choi, and H. Neuhaus, "Peroral cholangioscopy: diagnostic and therapeutic applications," *Gastroenterology*, vol. 144, no. 2, pp. 276–282, 2013.

[5] M. Nakajima, Y. Akasaka, K. Fukumoto et al., "Peroral pancreatoscopy under duodenoscopic guindance," *The American Journal of Gastroenterology*, vol. 166, pp. 241–247, 1976.

[6] T. Itoi, J. H. Moon, and I. Waxman, "Current status of direct peroral cholangioscopy," *Dig Endoscopy*, supplment 1, pp. 154–157, 2011.

[7] K. Kawai, M. Nakajima, Y. Akasaka, K. Shimamotu, and K. Murakami, "A new endoscopic method: the peroral choledocho pancreatoscopy," *Leber Magen Darm*, vol. 6, no. 2, pp. 121–124, 1976.

[8] Y. Urakami, E. Seifert, and H. Butke, "Peroral direct cholangioscopy (PDCS) using routine straight-view endoscope: first report," *Endoscopy*, vol. 9, no. 1, pp. 27–30, 1977.

[9] R. J. Shah, D. G. Adler, J. D. Conway et al., "Cholangiopancreatoscopy," *Gastrointestinal Endoscopy*, vol. 68, no. 3, pp. 411–421, 2008.

[10] M. Ramchandani, D. N. Reddy, S. Lakhtakia et al., "Per oral cholangiopancreatoscopy in pancreatico biliary diseases—expert consensus statements," *World Journal of Gastroenterology*, vol. 21, no. 15, pp. 4722–4734, 2015.

[11] R. J. Shah, "Innovations in intraductal endoscopy: cholangioscopy and pancreatoscopy," *Gastrointestinal Endoscopy Clinics of North America*, vol. 25, no. 4, pp. 779–792, 2015.

[12] M. A. Parsi, T. Stevens, A. Bhatt, S. Jang, and J. J. Vargo, "Digital, catheter-based single-operator cholangiopancreatoscopes: can pancreatoscopy and cholangioscopy become routine procedures?" *Gastroenterology*, vol. 149, no. 7, pp. 1689–1690, 2015.

[13] A. Cannavale, M. Bezzi, F. Cereatti et al., "Combined radiological-endoscopic management of difficult bile duct stones: 18-year single center experience," *Therapeutic Advances in Gastroenterology*, vol. 8, no. 6, pp. 340–351, 2015.

[14] S. Ghersi, L. Fuccio, M. Bassi et al., "Current status of peroral cholangioscopy in biliary tract diseases," *World Journal of Gastrointestinal Endoscopy*, vol. 7, no. 5, pp. 510–517, 2015.

[15] I. Yasuda and T. Itoi, "Recent advances in endoscopic management of difficult bile duct stones," *Digestive Endoscopy*, vol. 25, no. 4, pp. 376–385, 2013.

[16] G. Trikudanathan, M. A. Arain, R. Attam, and M. L. Freeman, "Advances in the endoscopic management of common bile duct stones," *Nature Reviews Gastroenterology and Hepatology*, vol. 11, no. 9, pp. 535–544, 2014.

[17] P. Massinha, N. Nunes, R. Liberal et al., "Usefulness of direct peroral cholangioscopy in the management of intrahepatic lithiasis," *Endoscopy*, vol. 46, supplement 1, article E553, 2014.

[18] Y.-H. Yeh, M.-H. Huang, J.-C. Yang, L.-R. Mo, J. Lin, and S.-K. Yueh, "Percutaneous trans-hepatic cholangioscopy and lithotripsy in the treatment of intrahepatic stones: a study with 5 year follow-up," *Gastrointestinal Endoscopy*, vol. 42, no. 1, pp. 13–18, 1995.

[19] D. C. Kim, J. H. Moon, H. J. Choi, M. H. Choi, T. H. Lee, and S.-W. Cha, "Successful endoscopic treatment for Mirizzi syndrome type II under direct peroral cholangioscopy using an ultraslim upper endoscope," *Endoscopy*, vol. 46, supplement 1, pp. E103–E104, 2014.

[20] H. Issa, B. Bseiso, and A. H. Al-Salem, "Successful laser lithotripsy using peroral SpyGlass cholangioscopy in a patient with Mirizzi syndrome," *Endoscopy*, vol. 43, supplement 2, pp. E166–E167, 2011.

[21] T. Tsuyuguchi, H. Saisho, T. Ishihara, T. Yamaguchi, and E. K. Onuma, "Long-term follow-up after treatment of Mirizzi syndrome by peroral cholangioscopy," *Gastrointestinal Endoscopy*, vol. 52, no. 5, pp. 639–644, 2000.

[22] K. F. Binmoeller, F. Thonke, and N. Soehendra, "Endoscopic treatment of Mirizzi's syndrome," *Gastrointestinal Endoscopy*, vol. 39, no. 4, pp. 532–536, 1993.

[23] J. Roque, S. H. Ho, N. Reddy, and K. L. Goh, "Endoscopic ablation therapy for biliopancreatic malignancies," *Clinical Endoscopy*, vol. 48, no. 1, pp. 15–19, 2015.

[24] M. E. J. Ortner, K. Caca, F. Berr et al., "Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study," *Gastroenterology*, vol. 125, no. 5, pp. 1355–1363, 2003.

[25] A. Tyberg, S. Zerbo, R. Z. Sharaiha, and M. Kahaleh, "Digital cholangioscopy: assessing the impact of radiofrequency ablation," *Endoscopy*, vol. 47, no. 1, article E544, 2015.

[26] S. H. Noh, H. Park do, Y. R. Kim et al., "Peroral direct cholangioscopic-guided biopsy and photodynamic therapy using an ultraslim upper endoscope for recurrent hepatocellular carcinoma with intraductal tiny nodular tumor growth," *Gut and Liver Journal*, vol. 4, no. 3, pp. 398–401, 2010.

[27] P. Montemaggi, G. Costamagna, R. R. Dobelbower et al., "Intraluminal brachytherapy in the treatment of pancreas and bile duct carcinoma," *International Journal of Radiation Oncology, Biology, Physics*, vol. 32, no. 2, pp. 437–443, 1995.

[28] F. Deodato, G. Clemente, G. C. Mattiucci et al., "Chemoradiation and brachytherapy in biliary tract carcinoma: long-term results," *International Journal of Radiation Oncology, Biology, Physics*, vol. 64, no. 2, pp. 483–488, 2006.

[29] M. Hasan, A. Canipe, B. Tharian, U. Navaneethan, S. Varadarajulu, and R. Hawes, "Digital cholangioscopy-directed removal of a surgical staple from a strictured bile duct," *Gastrointestinal Endoscopy*, vol. 82, no. 5, p. 958, 2015.

[30] J. C. Wong, M. Y. Wong, K. L. Lam, and J. Y. Lau, "Second-generation peroral cholangioscopy and holmium: YAG laser lithotripsy for rescue of impacted biliary stone extraction basket," *Gastrointestinal Endoscopy*, vol. 83, no. 4, pp. 837–838, 2016.

[31] T. Tsuchiya, T. Itoi, A. Sofuni, S. Tsuji, and N. Ikeuchi, "Rescue of basket-impacted stone by use of electrohydraulic lithotripsy under cholangioscopy," *Gastrointestinal Endoscopy*, vol. 79, no. 3, p. 376, 2014.

[32] D. V. Sejpal, A. S. Vamadevan, and A. J. Trindade, "Removal of an embedded, migrated plastic biliary stent with the use of cholangioscopy," *Gastrointestinal Endoscopy*, vol. 81, no. 6, pp. 1482–1483, 2015.

[33] M. R. Sanaka, V. Wadhwa, and M. Patel, "Retrieval of proximally migrated biliary stent with direct peroral cholangioscopy with an ultraslim endoscope," *Gastrointestinal Endoscopy*, vol. 81, no. 6, pp. 1483–1484, 2015.

[34] T. Ikeura, M. Shimatani, M. Takaoka, M. Masuda, K. Hayashi, and K. Okazaki, "Reintervention for an occluded metal stent under the guidance of peroral direct cholangioscopy by using an ultra-slim enteroscope," *Gastrointestinal Endoscopy*, vol. 81, no. 1, pp. 226–227, 2015.

[35] M. A. Parsi, "Peroral cholangioscopy-assisted guidewire placement for removal of impacted stones in the cystic duct remnant," *World Journal of Gastrointestinal Surgery*, vol. 1, no. 1, pp. 59–61, 2009.

[36] J. U. Shin, J. K. Lee, K. M. Kim et al., "Endoscopic nasogallbladder drainage by using cholangioscopy for acute cholecystitis combined with cholangitis or choledocholithiasis (with video)," *Gastrointestinal Endoscopy*, vol. 76, no. 5, pp. 1052–1055, 2012.

[37] A. Tyberg, S. Zerbo, M. Kahaleh et al., "Digital cholangioscopy-assisted gallbladder drainage: seeing is accessing," *Endoscopy*, vol. 47, supplement 1, p. E417, 2015.

[38] E. Gutkin, S. A. Hussain, and S. H. Kim, "The successful treatment of chronic cholecystitis with SpyGlass cholangioscopy-assisted gallbladder drainage and irrigation through self-expandable metal stents," *Gut and Liver*, vol. 6, no. 1, pp. 136–138, 2012.

[39] T. Itoi, N. Coelho-Prabhu, and T. H. Baron, "Endoscopic gallbladder drainage for management of acute cholecystitis," *Gastrointestinal Endoscopy*, vol. 71, no. 6, pp. 1038–1045, 2010.

[40] Y. Komaki, S. Kanmura, K. Funakawa et al., "A case of hereditary hemorrhagic telangiectasia with repeated hemobilia arrested by argon plasma coagulation under direct peroral cholangioscopy," *Gastrointestinal Endoscopy*, vol. 80, no. 3, pp. 528–529, 2014.

[41] M. Aydinli, I. Koruk, S. Koruk et al., "Intraoperative cholangioscopy with an ultrathin endoscope for hemobilia," *Endoscopy*, vol. 43, supplement 2, p. E410, 2011.

[42] H.-H. Yen, C.-W. Yang, and Y.-Y. Chen, "Direct cholangioscopy using an ultrathin endoscope for the diagnosis of hemobilia," *Digestive Endoscopy*, vol. 26, no. 3, pp. 497–498, 2014.

[43] E. G. Moura, T. Franzini, R. N. Moura et al., "Cholangioscopy in bile duct disease: a case series," *Arquivos de Gastroenterologia*, vol. 51, pp. 250–254, 2014.

[44] G. Terheggen and H. Neuhaus, "New options of cholangioscopy," *Gastroenterology Clinics of North America*, vol. 39, no. 4, pp. 827–844, 2010.

[45] T. Franzini, R. Moura, G. Rodela et al., "A novel approach in benign biliary stricture—balloon dilation combined with cholangioscopy-guided steroid injection," *Endoscopy*, vol. 47, supplement 1, pp. E571–E572, 2015.

[46] T. Shimizu, T. Urahashi, Y. Ihara et al., "Successful treatment of severe anastomotic stricture of a choledochojejunostomy after living donor liver transplantation with transhepatic cholangioscopy-guided balloon dilatation," *Transplantation Proceedings*, vol. 46, no. 3, pp. 999–1000, 2014.

[47] Y. S. Woo, J. K. Lee, D. H. Noh, J. K. Park, K. H. Lee, and K. T. Lee, "SpyGlass cholangioscopy-assisted guidewire placement for post-LDLTbiliary strictures: a case series," *Surgical Endoscopy*, 2015.

[48] M. A. Parsi, J. Guardino, and J. J. Vargo, "Peroral cholangioscopy-guided stricture therapy in living donor liver transplantation," *Liver Transplantation*, vol. 15, no. 2, pp. 263–265, 2009.

[49] U. Navaneethan, P. G. K. Venkatesh, M. Al Mohajer, and A. Gelrud, "Successful diagnosis and management of biliary cast syndrome in a liver transplant patient using single operator cholangioscopy," *Journal of the Pancreas*, vol. 12, no. 5, pp. 461–463, 2011.

[50] D. Balderramo, O. Sendino, R. Miquel et al., "Prospective evaluation of single-operator peroral cholangioscopy in liver transplant recipients requiring an evaluation of the biliary tract," *Liver Transplantation*, vol. 19, no. 2, pp. 199–206, 2013.

[51] A. Gürakar, H. Wright, C. Camci, and N. Jaboour, "The application of SpyScope® technology in evaluation of pre and post liver transplant biliary problems," *Turkish Journal of Gastroenterology*, vol. 21, no. 4, pp. 428–432, 2010.

[52] N. S. Awadallah, Y. K. Chen, C. Piraka, M. R. Antillon, and R. J. Shah, "Is there a role for cholangioscopy in patients with primary sclerosing cholangitis?" *The American Journal of Gastroenterology*, vol. 101, no. 2, pp. 284–291, 2006.

[53] U. Arnelo, E. von Seth, and A. Bergquist, "Prospective evaluation of the clinical utility of single-operator peroral cholangioscopy in patients with primary sclerosing cholangitis," *Endoscopy*, vol. 47, no. 8, pp. 696–702, 2015.

[54] A. Siiki, I. Rinta-Kiikka, T. Koivisto, K. Vasama, J. Sand, and J. Laukkarinen, "Spyglass single-operator peroral cholangioscopy seems promising in the evaluation of primary sclerosing cholangitis-related biliary strictures," *Scandinavian Journal of Gastroenterology*, vol. 49, no. 11, pp. 1385–1390, 2014.

[55] E. Kalaitzakis, R. Sturgess, H. Kaltsidis et al., "Diagnostic utility of single-user peroral cholangioscopy in sclerosing cholangitis," *Scandinavian Journal of Gastroenterology*, vol. 49, no. 10, pp. 1237–1244, 2014.

[56] T. Itoi, T. Kamisawa, Y. Igarashi et al., "The role of peroral video cholangioscopy in patients with IgG4-related sclerosing cholangitis," *Journal of Gastroenterology*, vol. 48, no. 4, pp. 504–514, 2013.

[57] J. J. Tischendorf, M. Krüger, C. Trautwein et al., "Cholangioscopic characterization of dominant bile duct stenoses in patients with primary sclerosing cholangitis," *Endoscopy*, vol. 38, no. 7, pp. 665–669, 2006.

Hindawi Publishing Corporation
Gastroenterology Research and Practice
Volume 2016, Article ID 6153893, 5 pages
http://dx.doi.org/10.1155/2016/6153893

Clinical Study

Short-Term Biliary Stent Placement Contributing Common Bile Duct Stone Disappearance with Preservation of Duodenal Papilla Function

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Received 9 December 2015; Accepted 18 April 2016

Academic Editor: Sooraj Tejaswi

Aims. To investigate the effect of biliary stent placement without endoscopic sphincterotomy (EST) on common bile duct stones (CBDS) disappearance and the contribution of preserving the duodenal papilla function to reduce recurrence of CBDS. *Methods*. Sixty-six patients admitted for acute obstructive cholangitis due to CBDS who underwent biliary stent placement without EST for 2 years from March 2011 were evaluated retrospectively. The second endoscopic retrograde cholangiopancreatography (ERCP) was performed for treatment of CBDS 3 to 4 months after the first ERCP. We estimated the rate of stone disappearance at the time of second ERCP. *Results*. CBDS disappearance was observed in 32 (48.5%) of 66 patients. The diameter of the bile ducts and the diameter of CBDS in patients with CBDS disappearance were significantly smaller than in those with CBDS requiring extraction ($p = 0.007$ and $p < 0.001$, resp.). Stone disappearance was evident when the diameter of bile ducts and that of CBDS were <10 and 7 mm, respectively ($p = 0.002$). *Conclusions*. Short-term stent placement without EST eliminates CBDS while preserving duodenal papilla function and may be suitable for treating CBDS in patients with nondilated bile ducts and small CBDS.

1. Introduction

To treat common bile duct stones (CBDS), endoscopic sphincterotomy (EST) is an established procedure and is widely performed. However, late complications including liver abscess, cholangitis, CBDS recurrence, and bile duct cancer have recently been reported with this technique [1, 2], the occurrence of which is probably due to reflux into the bile duct of duodenal juice, which contains both pancreatic juice and bacteria. It is desirable to avoid such complications in younger patients, who have a long life expectancy.

Endoscopic papillary balloon dilation is an alternative method for treatment of CBDS [3], and it has the advantage of preserving duodenal papillary function [4]. However, compared with EST, a higher rate of postendoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) has been reported [4], and this remains a potential hazard when using this method for treatment of CBDS.

Biliary stent placement is widely performed for acute obstructive cholangitis (AOC) due to CBDS. This procedure is easy to perform, effective, and accepted as an emergent treatment [5, 6]. In patients with difficult stones, biliary stent placement to drain obstructed bile juice due to CBDS can be selected [7–10]. Some reports have described a decrease in size and diameter, as well as disappearance of stones in patients with biliary stent placement after EST [7, 8].

We performed biliary stent placement in patients of various ages for AOC due to CBDS without EST during their first hospitalization. These patients were discharged temporarily after evidence of relief of AOC, and readmission for extraction of CBDS was scheduled 3 to 4 months after

Table 1: Patient characteristics ($n = 66$).

Characteristics	n
Male/female	43/23
Mean age (years)	68.5 (36–94)
Cholangitis	
Grade III/II/I	3/24/39
Gallbladder with/without gallstones	45/14

Table 2: Stone disappearance ($n = 66$).

Stone disappearance/persistence (n)	32/34
Stone disappearance rate (%)	48.5

the first hospitalization. When endoscopic treatments were initiated at the second hospitalization, stone disappearance occurred in about half of patients. Herein, we report our findings in these patients.

2. Subjects and Methods

Sixty-six patients admitted for AOC due to CBDS who underwent biliary stent placement for 2 years from March 2011 were evaluated retrospectively. Patients with a past history of EST and biliary tract malignancies such as gallbladder carcinoma or bile duct carcinoma were excluded. Of the 66 patients, 43 were male and 23 were female. The mean age of these patients was 68.5 years (range: 36–94 years) (Table 1). Severity of AOC was confirmed in accordance with the 2013 Tokyo Guidelines [11]. Severity grades III, II, and I were noted in 3, 24, and 39 patients, respectively. Of the 59 patients with a gallbladder, 45 had gallbladder stones. This retrospective study was approved by the institutional review board of Shizuoka General Hospital.

Diagnosis of CBDS was confirmed by recognition of a movable filling defect on endoscopic retrograde cholangiopancreatography (ERCP), and a 7 Fr/7 cm double-pigtail stent (Olympus, Japan) was placed in all of these patients. Biliary stent placement was performed with a lateral-viewing endoscope (JF 260, Olympus, Japan). Bile duct diameter and CBDS were measured using ERCP images. After cannulating a bile duct, a small amount of contrast medium (60% Urographin, Bayer) was injected and CBDS was identified, followed by selective cannulation of the relevant bile duct. Bile juice was aspirated as much as possible, and a cholangiogram showing intrahepatic bile ducts and a cystic duct was recorded. After cholangiography, a 0.035-inch guide wire (Jagwire, Boston Scientific Japan) was inserted. The 7 Fr/7 cm double-pigtail biliary stent was placed over the guide-wire with the objective of fixing the tip of the stent to either hepatic duct. A pancreatic stent was placed simultaneously in cases where difficulty placing the cannula selectively extended the procedure time beyond 10 minutes, misinjection into the pancreatic duct occurred more than 3 times, or a small orifice in the major papilla was present.

Oral food intake was started on the day after stent placement, if symptoms of AOC such as pain, fever, and abnormal laboratory data were relieved. Patients were discharged temporarily if aggravation of AOC was not recognized after starting oral food intake. Readmission was scheduled for endoscopic treatment of CBDS 3 to 4 months after the first hospitalization. In patients with gallstones, cholecystectomy was performed before the second admission.

With the second ERCP, identification of CBDS was achieved by cholangiography while maintaining a biliary stent in the bile duct. When a filling defect revealing CBDS was absent, the biliary stent was removed and treatment for CBDS was terminated. On the other hand, when a filling defect showing CBDS was recognized, extraction of CBDS using a basket catheter was performed after removing the biliary stent with EST, or without EST because of small diameter of the stone. In patients treated with an anticoagulant, the biliary stent was maintained in place.

We estimated the rate of stone disappearance and compared diameters of bile ducts, diameters of CBDS, number of CBDS, ratio of calcified CBDS to total CBDS, and duration from discharge to second admission in the 2 groups (i.e., those with stone disappearance and stone persistence). Stone disappearance was confirmed by ERCP. Complications associated with endoscopic procedures were evaluated. The recurrence rate of CBDS after the second ERCP with an average follow-up period of 34.3 months (9–44 months) was estimated, while recurrence of CBDS was evaluated with recurrence of symptoms of cholangitis.

The data obtained in this study were statistically analyzed by Student's t-test and Fisher's exact test to determine factors related to stone disappearance. p values <0.05 were regarded as statistically significant.

3. Results

CBDS disappeared in 32 (48.5%) of 66 patients (Table 2). Diameters of the bile ducts and the diameter of CBDS in patients with stone disappearance (Table 3) were significantly smaller than in those without stone disappearance ($p = 0.007$ and $p < 0.001$, resp.). The number of stones, ratio of calcified stones, and duration from first hospitalization discharge to second admission were not significantly different between the 2 groups ($p = 0.998$, $p = 0.180$, and $p = 0.205$, resp.). Seventeen patients had bile duct and CBDS diameters of <10 and 7 mm, respectively (Table 4). CBDS disappeared in 14 (82.4%) of the 17 patients. When the diameters of the bile duct and stones were <10 and 7 mm, respectively, CBDS disappeared readily ($p = 0.002$).

With respect to complications (Table 5), mild post-ERCP pancreatitis and middle hepatic vein thrombosis were experienced in 4 (6.1%) patients and 1 (1.5%) patient, respectively. The latter complication was caused by compression of the middle hepatic vein by the tip of the stent placed at the caudal lobe.

During the second ERCP (Table 6), 32 patients with stone disappearance underwent biliary stent removal and the treatment for CBDS was completed. Among patients without stone disappearance, stone extraction using a basket

Table 3: Analysis of factors associated with stone disappearance and persistence ($n = 66$).

	CBDS disappearance ($n = 32$)	CBDS persistence ($n = 34$)	p value
Diameter of bile ducts (mm)	9.59 ± 3.43	12.20 ± 4.17	0.007
Diameter of bile duct stones (mm)	5.77 ± 3.01	11.21 ± 6.42	<0.001
Number of bile duct stones (pieces)	1.56 ± 0.98	1.55 ± 1.02	0.988
Ratio of calcified stones (%)	75.8	91.1	0.180
Duration from first hospitalization discharge to second admission (days)	143 ± 10	111 ± 58	0.205

Table 4: Stone disappearance in patients with CBD < 10 mm and CBDS < 7 mm.

	Diameter		p value
	CBD < 10 mm and CBDS < 7 mm	CBD ≥ 10 mm or CBDS ≥ 7 mm	
CBDS disappearance	14/17 (82.4%)	18/49 (36.7%)	0.002

Table 5: Complications.

Complications	n (%)
Mild pancreatitis	4 (6.1)
Hepatic vein thrombosis	1 (1.5)

catheter with EST was performed in 17 (25.8%) patients and stone extraction using a basket catheter without EST because of small stone diameter and a widely opened papilla orifice due to stent placement (phenomenon which was frequently experienced in our study) was performed in 10 (15.1%) patients. Biliary stent replacement, for persistent biliary stent placement due to a large stone, and anticoagulant administration were performed in 7 (10.6%) patients. Finally, CBDS were treated without disruption of duodenal papilla function in 42 (63.6%) patients (Figure 1).

During an average follow-up period of 34.3 months (Table 6), cholangitis due to stone recurrence was experienced in 1 (3.1%) patient with stone disappearance, 2 (11.8%) patients with EST, and 1 (10%) patient with stone extraction without EST. However, the recurrence rate of cholangitis was not significantly different between the two groups: stone disappearance or stone extraction by a basket catheter without EST and stone extraction with EST ($p = 0.57$).

4. Discussion

Several studies have investigated stent placement for the treatment of CBDS in cases with stones that cannot be removed by ordinary endoscopic treatments including EST [7–10]. In one report, plastic stent placement was evaluated for the treatment of large CBDS in 45 patients [7]. Among all 45 patients, EST was performed in cases where extraction of CBDS failed. A decrease in the size of stones was observed in almost all patients and CBDS disappearance occurred in 22.2% of patients. Agitation of CBDS within the bile duct where the stent was located was suggested to be the most likely explanation for these results. In another report [8], placement of a pigtail stent after EST resulted in disappearance in 7 (35%) of 20 patients and a decrease in the size of CBDS in 11 (55%) of 20 patients, presumably caused by grinding of the placed stent against the stone.

Stent placement for 2 months was reported to contribute to a decrease in the number and size of CBDS in almost all of a cohort of 40 patients who did not undergo EST [9]. CBDS diameters were greater than 20 mm in many patients; moreover, disappearance of small CBDS was observed. The authors presumed that disruption of stones caused by the placed stent contributed to a decrease in CBDS diameters and numbers. Friability of stones was also described as a possible mechanism over the short term, resulting in facilitation of endoscopic procedures using a lithotriptor for CBDS [12]. Agitation, grinding, and friability of stones might contribute to the destruction of CBDS, enabling them to be discharged, and preserving duodenal papilla function in patients who have not undergone EST is also considered to be responsible for disappearance of small CBDS by facilitating their discharge. In another report, discharge of CBDS with preservation of the duodenal papilla was observed during ERCP [13]. This suggests that discharge of CBDS is a possible mechanism for CBDS disappearance.

In our study, CBDS disappeared with short-term stent placement for about 3 months without EST in about 50% of patients. Smaller sizes of CBD and CBDS were associated with CBDS disappearance. Short-term stent placement could contribute to CBDS disappearance, especially in patients with CBD diameters of <10 mm and CBDS diameters of <7 mm. The most likely mechanism of the disappearance in our cases was discharge of CBDS through the functional duodenal papilla, in addition to agitation caused by the placed stent. This is because the smaller CBDS would be discharged more readily through the duodenal papilla and the smaller bile duct could be associated with preserved bile excretion function of the duodenal papilla and probably with CBDS discharge.

Previous studies differ from ours in that the endoscopic treatments used for patients in those studies, including EST, were not successful in removing the stones. In our patients,

Table 6: Procedures during the second ERCP and cholangitis after the second ERCP.

	Procedures during the second ERCP	n (%)	Cholangitis n (%)
Stone disappearance	Biliary stent removal	32 (48.5)	1 (3.1)[#]
Stone persistence	Stone extraction with EST	17 (25.8)	2 (11.8)[#]
	Stone extraction by a basket catheter without EST	10 (15.1)	1 (10)[#]
	Biliary stent replacement for persistent biliary stent placement	7 (10.6)	3 (42.9)

[#] $p = 0.57$.
shows statistical significance between "Biliary stent removal" plus "Stone extraction by a basket catheter without EST", and "Stone extraction with EST".

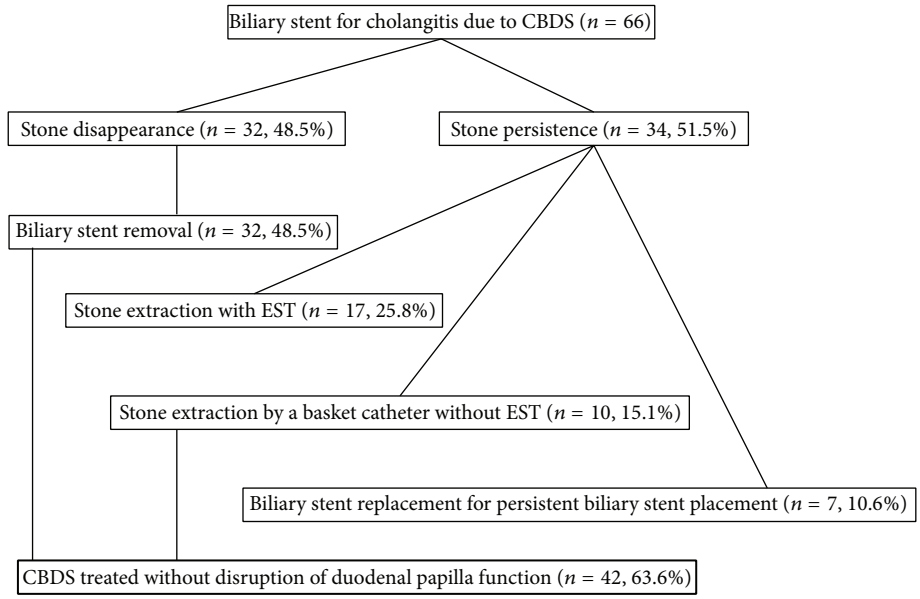

Figure 1: Flow diagram of patients analyzed in this study.

we did not attempt to remove CBDS by EST before stent placement, and we did not always encounter stones that were difficult to treat. These factors could have contributed to the higher rate of stone disappearance in our study compared with previous reports.

Although EST is widely performed to treat CBDS, complications including perforation, hemorrhage, and pancreatitis are experienced during or after the procedure [14, 15]. Moreover, disruption of the duodenal papilla lets the duodenal juice, including pancreatic juice and bacteria, reflux into the bile duct, which can induce liver abscess, cholangitis, and CBDS recurrence as late complications [1, 2]. Our results showed that recurrent cholangitis during an average follow-up period of 34.3 months occurred in 11.8% of patients with EST as the second ERCP procedure, while, compared with a group of patients who did not undergo EST because of stone disappearance or stone extraction without EST following biliary stent placement, the recurrence rate of cholangitis was not significantly different. However, the follow-up period was too short to estimate complications correctly.

Our method compelled patients to be admitted twice. In spite of the fact, the advantage of our method is the preservation of duodenal papilla function. Moreover, if the size of bile duct and CBDS is <10 and 7 mm, respectively, the disappearance rate is high and statistically significant. Patients that meet these criteria have the potential to experience great benefit with the procedure. In particular, younger patients with bile duct size and CBDS <10 and 7 mm, respectively, may be ideal candidates, because they have a long life expectancy and avoiding destruction of the duodenal papilla function would therefore be highly desirable.

We propose the following new strategy for CBDS treatment. For younger patients with CBD diameters of <10 mm and CBDS diameters of <7 mm, a biliary stent is placed temporarily for 3 months and a second ERCP is performed. If the CBDS disappears, the treatment is considered complete and the stent is removed. Patients with relatively large persistent stones would be indicated to undergo EST with stone extraction. In those with small but persistent stones, EST would not be needed for stone extraction.

We deemed that stones had disappeared by confirming the absence of a filling defect on ERCP. This is a typical method used to judge stone disappearance. Persistent stones cannot be excluded completely by ERCP if they are small in diameter. However, our results showed that even if small stones remained that could not be confirmed on ERCP, they

would not be of clinical importance, because no cases of cholangitis occurred after the second ERCP in patients whose stones were judged to have disappeared.

5. Conclusions

Our study suggests that short-term stent placement without EST is effective for the treatment of CBDS with preservation of duodenal papilla function. Suitable initial candidates for this method of treatment are patients with nondilated bile ducts and small CBDS. Further study is warranted to confirm our results, because this study was limited by a small sample size and was performed at a single center.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contributions

Study conception and design were conducted by M. Kikuyama. Acquisition of data was conducted by T. Kurokami. Y. Kodama contributed to analysis and interpretation of data. T. Ueda contributed to drafting of the paper.

References

[1] I. Yasuda, N. Fujita, H. Maguchi et al., "Long-term outcomes after endoscopic sphincterotomy versus endoscopic papillary balloon dilation for bile duct stones," *Gastrointestinal Endoscopy*, vol. 72, no. 6, pp. 1185–1191, 2010.

[2] A. Tocchi, G. Mazzoni, G. Liotta, L. Lepre, D. Cassini, and M. Miccini, "Late development of bile duct cancer in patients who had biliary-enteric drainage for benign disease: a follow-up study of more than 1,000 patients," *Annals of Surgery*, vol. 234, no. 2, pp. 210–214, 2001.

[3] M. Staritz, K. Ewe, and K.-H. Meyer zum Büschenfelde, "Endoscopic papillary dilatation, a possible alternative to endoscopic papillotomy," *The Lancet*, vol. 319, no. 8284, pp. 1306–1307, 1982.

[4] T. H. Baron and G. C. Harewood, "Endoscopic balloon dilation of the biliary sphincter compared to endoscopic biliary sphincterotomy for removal of common bile duct stones during ERCP: a metaanalysis of randomized, controlled trials," *The American Journal of Gastroenterology*, vol. 99, no. 8, pp. 1455–1460, 2004.

[5] S. R. Cairns, L. Dias, P. B. Cotton, P. R. Salmon, and R. C. G. Russell, "Additional endoscopic procedures instead of urgent surgery for retained common bile duct stones," *Gut*, vol. 30, no. 4, pp. 535–540, 1989.

[6] E. C. S. Lai, F. P. T. Mok, E. S. Y. Tan et al., "Endoscopic biliary drainage for severe acute cholangitis," *The New England Journal of Medicine*, vol. 326, no. 24, pp. 1582–1586, 1992.

[7] Z. Fan, R. Hawes, C. Lawrence, X. Zhang, X. Zhang, and W. Lv, "Analysis of plastic stents in the treatment of large common bile duct stones in 45 patients," *Digestive Endoscopy*, vol. 23, no. 1, pp. 86–90, 2011.

[8] S. K. Jain, R. Stein, M. Bhuva, and M. J. Goldberg, "Pigtail stents: an alternative in the treatment of difficult bile duct stones," *Gastrointestinal Endoscopy*, vol. 52, no. 4, pp. 490–493, 2000.

[9] A. Horiuchi, Y. Nakayama, M. Kajiyama et al., "Biliary stenting in the management of large or multiple common bile duct stones," *Gastrointestinal Endoscopy*, vol. 71, no. 7, pp. 1200–1203, 2010.

[10] E. Slattery, V. Kale, W. Anwar, G. Courtney, and A. R. Aftab, "Role of long-term biliary stenting in choledocholithiasis," *Digestive Endoscopy*, vol. 25, no. 4, pp. 440–443, 2013.

[11] S. Kiriyama, T. Takada, S. M. Strasberg et al., "TG13 guidelines for diagnosis and severity grading of acute cholangitis (with videos)," *Journal of Hepato-Biliary-Pancreatic Sciences*, vol. 20, no. 1, pp. 24–34, 2013.

[12] S. S. Sharma, A. Jhajharia, and S. Maharshi, "Short-term biliary stenting before mechanical lithotripsy for difficult bile duct stones," *Indian Journal of Gastroenterology*, vol. 33, no. 3, pp. 237–240, 2014.

[13] T. Itoi, N. Ikeuchi, A. Sofuni, F. Itokawa, and T. Kurihara, "Spontaneous passage of bile duct stone, mimicking laying an egg (with video)," *Gastrointestinal Endoscopy*, vol. 69, no. 7, pp. 1389–1390, 2009.

[14] M. L. Freeman, D. B. Nelson, S. Sherman et al., "Complications of endoscopic biliary sphincterotomy," *The New England Journal of Medicine*, vol. 335, no. 13, pp. 909–918, 1996.

[15] P. B. Cotton, D. A. Garrow, J. Gallagher, and J. Romagnuolo, "Risk factors for complications after ERCP: a multivariate analysis of 11,497 procedures over 12 years," *Gastrointestinal Endoscopy*, vol. 70, no. 1, pp. 80–88, 2009.

Hindawi Publishing Corporation
Gastroenterology Research and Practice
Volume 2016, Article ID 7675953, 10 pages
http://dx.doi.org/10.1155/2016/7675953

Research Article

Factor Analysis Influencing Postoperative Hospital Stay and Medical Costs for Patients with Definite, Suspected, or Unmatched Diagnosis of Acute Cholecystitis according to the Tokyo Guidelines 2013

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Received 20 October 2015; Revised 6 February 2016; Accepted 28 March 2016

Academic Editor: Mohammed Nabil Quraishi

Purpose. To identify significant independent preoperative factors influencing postoperative hospital stay (PHS) and medical costs (MC) in 171 patients who underwent cholecystectomy for benign gallbladder diseases and had definite, suspected, or unmatched acute cholecystitis (AC) diagnosis according to the Tokyo Guidelines 2013 (TG13). *Methods.* The 171 patients were classified according to the combination of diagnostic criteria including local signs of inflammation (A), systemic signs of inflammation (B), and imaging findings (C): A+ B+ C (definite diagnosis, $n = 84$), A+ B (suspected diagnosis, $n = 25$), (A or B) + C ($n = 10$), A ($n = 41$), and B ($n = 11$). *Results*. The A+ B + C and (A or B) + C groups had equivalent PHS and MC, suggesting that imaging findings were essential for AC diagnosis. PHS and MC were significantly increased in the order of severity grades based on TG13. Performance status (PS), white blood cell count, and severity grade were identified as preoperative factors influencing PHS by multivariate analysis, and significant independent preoperative factors influencing MC were age, PS, preoperative biliary drainage, hospital stay before surgery, albumin, and severity grade. *Conclusion*. PS and severity grade significantly influenced prolonged PHS and increased MC.

1. Introduction

Laparoscopic cholecystectomy (LC) has become the standard treatment for acute cholecystitis (AC) [1]; however, when AC becomes more severe, it increases the risk of major complications such as bile spillage, major bleeding, common bile duct injury, and bowel injury [2], resulting in prolonged postoperative hospital stay (PHS) [3]. The clinical features of patients with AC differ by disease severity; therefore, AC severity assessment is important in providing suitable medical management for each patient. Under these circumstances, the Evidence-Based Practice Guidelines for the Management of Acute Cholangitis and Cholecystitis were published in Japanese for the first time in 2005 (JG05) [4]. The Tokyo Guidelines 2007 were the first international practical guidelines (TG07) [5]. After the Revision Committee for TG07 performed multi-institutional studies and collected cases of acute cholangitis, AC, and noninflammatory biliary disease [6], TG07 was revised as the Tokyo Guidelines 2013 (TG13) [7].

LC is recognized as a cost-effective treatment for patients with AC compared with open cholecystectomy [8–10], and various factors influencing length of hospital stay including PHS and medical costs (MC) during hospitalization have been studied [3, 11, 12]. Identification of significant independent factors that affect PHS and MC in patients with AC

not only is beneficial for the quality management of patient medical treatment but also is useful to assess severity grading. No previous studies have focused on MC as an index to evaluate AC severity grading, although many studies of AC severity indices have used perioperative complications, major organ damage, and hospital stay [3, 13–16]. For the purpose of reducing MC in Japan, a new payment system based on the diagnosis procedure combination/Per-Diem Payment System (DPC/PDPS) [17] was developed and introduced in a medical treatment fee system in 2003 [18], and the DPC database recently became a feasible tool for the evaluation of care processes that can provide useful information contributing to improved medical treatment quality [19].

The AC diagnostic criteria consist of three major factors: local signs of inflammation (A), systemic signs of inflammation (B), and imaging findings (C). It is noteworthy that C is essential for the definite diagnosis of AC and that AC is suspected when A and B are present [20]. According to these criteria, however, some patients with C who are elderly and/or have dementia or paralysis are not definitively diagnosed with AC because they do not present with A or B [21]. Fever and elevated white blood cell count are not usually observed in elderly patients with AC because of their decreased antistress capacity [22, 23]. Recently, Zhang et al. [24] reported the significance of ultrasound examination in the elderly with AC because ultrasound score could accurately determine AC severity in the elderly. Therefore, the TG13 diagnostic criteria should be reassessed, especially in the elderly.

The mortality rate in patients with AC in the 1960s was comparatively high at 4% [25, 26]. However, since the 2000s, this rate decreased to <1% with improvements in medical treatment [27–29]. Therefore, mortality is no longer suitable as an indicator of AC prognosis in clinical practice, and we focused on PHS and MC as the clinical outcomes that should reflect AC severity. The aim of the present study was to identify the significant independent preoperative factors influencing PHS and MC in patients with definite, suspected, or unmatched AC diagnoses according to TG13, paying attention to the elderly and those with dementia who showed AC findings on imaging but lacked local or systemic signs of inflammation.

2. Materials and Methods

We reviewed the clinical database of 259 consecutive patients who underwent simple cholecystectomy for benign gallbladder diseases such as AC, adenomyomatosis, and benign polyps from January 2012 to July 2013 at Ise Red Cross Hospital. We excluded 57 patients who were treated conservatively at the first admission and operated after readmission and 31 without symptoms and/or findings of AC. Thus, we included 171 patients in the present study.

In our hospital, every in-hospital patient has his or her physical performance status assessed on admission by a nurse using the Criteria for Evaluating the Degree of Independence of Disabled Elderly Persons in Performing Activities of Daily Living [30], and it is recorded with the ranks of J, A, B, and C in electronic medical records. Therefore, we used these records for the assessment of physical performance, and these ranks could be translated into the performance status (PS) defined by the Eastern Cooperative Oncology Group [31], because ranks J, A, B, and C are compatible with PS 0 and 1, PS 2, PS 3, and PS 4, respectively. We defined PS 0, 1, 2, and 3 as "better" and PS 4 as "poor" in the present study.

2.1. AC Diagnostic Criteria and Severity Grading. We amassed diagnostic findings from electronic medical records and classified the patients with A (local signs of inflammation) + B (systemic signs of inflammation) + C (imaging findings) as definite diagnosis and those with A + B as suspected diagnosis based on the TG13 diagnostic criteria for AC (see the following list).

TG13 Diagnostic Criteria for AC. The criteria are as follows (TG13: Tokyo Guidelines 2013, AC: acute cholecystitis, RUQ: right upper quadrant, CRP: C-reactive protein, and WBC: white blood cell):

(A) local signs of inflammation and so forth:

(1) Murphy's sign,
(2) RUQ mass/pain/tenderness;

(B) systemic signs of inflammation and so forth:

(1) fever,
(2) elevated CRP,
(3) elevated WBC count;

(C) imaging findings:

imaging findings characteristic of AC.

Suspected diagnosis: one item in A + one item in B.

Definite diagnosis: one item in A + one item in B + C.

In the present study, new combinations—that is, the unmatched diagnoses of (one item in A or one item in B) + C and one item in A, B, or C—were added. The following list shows AC severity grades defined by TG13, which, in principle, should be employed for patients with definite AC diagnosis. In the present study, however, this severity grade was employed in the 171 patients with definite diagnoses as well as those with suspected or unmatched diagnosis as a matter of convenience.

AC Severity Assessment by TG13

Grade III. Grade III is associated with dysfunction of any one of the following organs/systems:

(1) Cardiovascular dysfunction*.
(2) Neurological dysfunction*.
(3) Respiratory dysfunction*.
(4) Renal dysfunction*.
(5) Hepatic dysfunction*.
(6) Hematological dysfunction*.

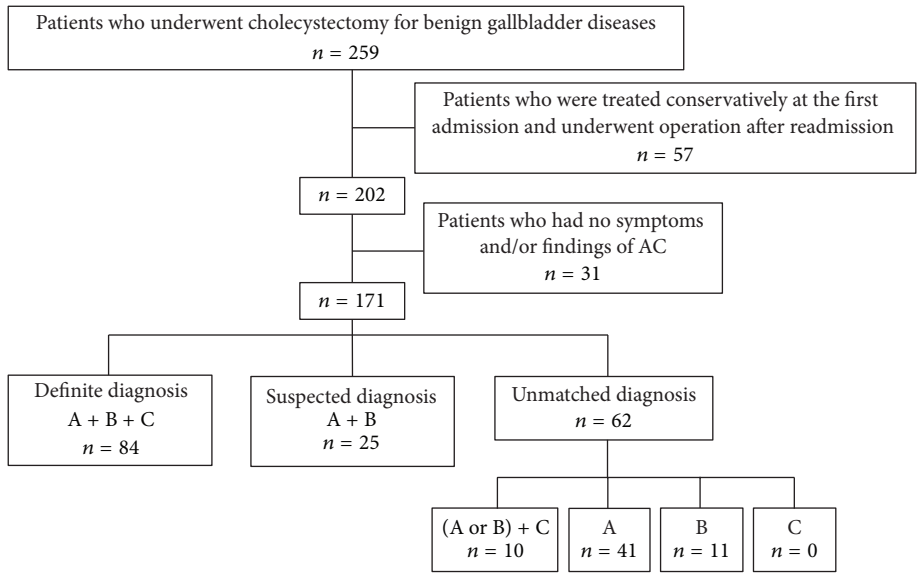

Figure 1: Flow diagram of the 259 patients who underwent cholecystectomy for benign gallbladder diseases according to the diagnostic criteria based on TG13. A, B, and C represent each item in the TG13 diagnostic criteria. AC: acute cholecystitis and TG13: Tokyo Guidelines 2013.

Grade II. Grade II is associated with any one of the following conditions:

(1) Elevated WBC (>18,000/mm^3).

(2) Palpable tender mass in the right upper abdominal quadrant.

(3) Duration of complaints > 72 h.

(4) Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, and emphysematous cholecystitis).

Grade I. Grade I does not meet the criteria of "Grade III" or "Grade II" AC:

AC: acute cholecystitis, TG13: Tokyo Guidelines 2013, and WBC: white blood cell.

*Details of criteria not described.

Figure 1 shows a flow diagram of the 259 patients who underwent cholecystectomy for benign gallbladder diseases. Of the subjects (171 patients), 84 patients were classified as having definite diagnosis (A + B + C); 25 suspected diagnosis (A + B); 62 unmatched diagnosis; 10 (A or B) + C; 41 A; and 11 B. No patients had only C.

2.2. Clinical Outcome Assessment. MC was calculated as the total amount of medical expenses during the hospital stay. To investigate the correlations between AC severity grading and MC, we used two different MC assessments: one was calculated by the fee-for-service (FFS) payment system and the other by the DPC system. The claim of medical expenses at our hospital was based on DPC/PDPS during the survey period.

2.3. Preoperative Factors Predicting Clinical Outcomes. To identify the preoperative factors predicting the clinical outcomes of patients with definite, suspected, or unmatched AC diagnoses, we accumulated preoperative clinical findings, including the severity grade based on TG13. These included (1) patient characteristics: age, sex, body mass index, history of diabetes mellitus, and PS; (2) preoperative diagnoses: gallbladder stones, CBD stones, acute cholangitis, and acute pancreatitis; (3) preoperative treatment: biliary drainage, hospital stay before surgery, and preoperative fasting period; (4) preoperative laboratory data: white blood cell count (WBC), hemoglobin, platelet cell count, C-reactive protein (CRP), serum albumin, blood urea nitrogen, serum creatinine, total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyl transpeptidase, serum amylase, and prothrombin time/international normalized ratio.

If patients had duplicate values in each item during the preoperative period, we selected the most unfavorable value for those patients. We determined the most useful preoperative factors to predict outcomes by using univariate and multivariate analyses.

2.4. Statistical Analysis. The data for continuous variables were expressed as mean values with standard deviations. The statistical significance of mean differences among the groups was determined by the Kruskal-Wallis test. In the evaluation of preoperative factors predicting clinical outcomes of AC (PHS and MC), simple regression analyses were first used to detect statistically significant associations between each preoperative factor and then a multiple linear regression analysis was used to identify the independent preoperative factors. Only factors that were statistically significant according to the univariate analysis were included in the multivariate analysis. The results were considered to be significant for values of $P < 0.05$.

Table 1: Characteristics and medical backgrounds for 171 patients who had definite, suspected, or unmatched AC diagnoses.

Variables	Total ($n = 171$)	A + B + C ($n = 84$)	A + B ($n = 25$)	(A or B) + C ($n = 10$)	A ($n = 41$)	B ($n = 11$)
Age (years)	64.2 ± 14.7	68.9 ± 13.5	58.1 ± 15.0	71.4 ± 17.9	57.2 ± 12.2	61.7 ± 10.0
Sex (male/female)	90/81	48/36	9/16	8/2	20/21	5/6
BMI (kg/m^2)	23.7 ± 3.3	23.6 ± 3.3	25.0 ± 3.7	22.6 ± 3.2	23.7 ± 3.3	23.6 ± 3.1
DM (yes/no)	23/148	11/73	1/24	3/7	7/34	1/10
PS (0, 1/2/3/4)	87/36/20/20	28/19/17/20	22/2/0/1	2/2/1/5	27/10/2/2	8/3/0/0
CT scan (yes/no)	171/0	84/0	25/0	10/0	41/0	11/0
Gallbladder stones (yes/no)	171/0	84/0	24/1	9/1	41/0	11/0
CBD stones (yes/no)	22/149	16/68	2/23	3/7	0/41	0/11
WBC ($\times 10^3/\mu L$)	10.1 ± 5.2	13.6 ± 4.8	6.7 ± 1.9	11.0 ± 4.3	5.6 ± 1.1	7.2 ± 2.4
Alb (g/dL)	3.7 ± 0.8	3.3 ± 0.7	4.2 ± 0.3	3.0 ± 1.1	4.2 ± 0.4	3.9 ± 0.5
CRP (mg/dL)	6.6 ± 9.3	12.1 ± 10.2	0.9 ± 1.2	8.6 ± 7.9	0.1 ± 0	0.3 ± 0.3
Definitive diagnosis of AC (yes/no)	84/87	84/0	0/25	0/10	0/41	0/11
Acute cholangitis (yes/no)	29/142	24/60	2/23	3/7	0/41	0/11
Preoperative biliary drainage (yes/no)	28/143	11/73	5/20	2/11	6/35	4/4
Hospital stay before surgery (day)	4.6 ± 6.2	6.9 ± 7.0	1.3 ± 1.0	9.2 ± 7.8	1.2 ± 0.8	2.7 ± 5.2
Surgical procedure (laparoscopic/conversion to open/open)	147/20/4	66/15/3	24/1/0	7/2/1	39/2/0	11/0/0
Length of operation (min)	108 ± 34	121 ± 33	98 ± 25	125 ± 49	89 ± 22	89 ± 23
Blood loss (mL)	152 ± 291	243 ± 310	14 ± 40	428 ± 585	18 ± 38	31 ± 39
Histopathology of gallbladder (cases)						
AC	52	47	0	4	1	0
Chronic cholecystitis	117	35	25	6	40	11
Other	2	2	0	0	0	0

AC: acute cholecystitis, BMI: body mass index, DM: diabetes mellitus, PS: performance status (Eastern Cooperative Oncology), CT: computed tomography, CBD: common bile duct, WBC: white blood cell, Alb: albumin, and CRP: C-reactive protein.

3. Results

The characteristics and medical backgrounds for 171 patients are shown in Table 1. Variables such as age, poor PS, WBC, CRP, acute cholangitis, hospital stay before surgery, and blood loss in the A + B + C and (A or B) + C groups were higher than those in the other groups. When we compared PHS and MC in the FFS system among the five groups of A + B + C (definite diagnosis), A + B (suspected diagnosis), (A or B) + C, A, and B, the A + B + C and (A or B) + C groups were equivalent, showing significantly higher values than the other groups (Figure 2). The backgrounds of 10 patients belonging to (A or B) + C were compared to those of 84 patients belonging to A + B + C. Regarding comorbidities in (A or B) + C, 5 patients (50%) had dementia (2 patients) or paralysis (3 patients). Among 84 patients in A + B + C, only 2 (2.4%) had dementia.

Regarding severity grade (Table 2), the 84 patients with definite diagnosis showed Grade I in 55 (65.5%), Grade II in 18 (21.4%), and Grade III in 11 (13.1%); all patients in A + B ($n = 25$), A ($n = 41$), and B ($n = 11$) belonged to Grade I. In contrast, among 10 patients with (A or B) + C, Grade I severity was noted in 7 (70%), Grade II in 2 (20%), and Grade III in 1 (10%). Postoperative complications with regard to severity grade for 171 patients are listed in Table 3.

Table 2: Distribution according to severity grades based on TG13 in the 171 patients who had definite, suspected, or unmatched AC diagnoses.

Combination of criteria	Grade I ($n = 139$)	Grade II ($n = 20$)	Grade III ($n = 12$)
Definite diagnosis			
A + B + C ($n = 84$)	55 (65.5%)	18 (21.4%)	11 (13.1%)
Suspected diagnosis			
A + B ($n = 25$)*	25 (100%)	0	0
Unmatched diagnosis			
(A or B) + C ($n = 10$)*	7 (70.0%)	2 (20.0%)	1 (10.0%)
A ($n = 41$)*	41 (100%)	0	0
B ($n = 11$)*	11 (100%)	0	0

*These patients were also classified according to severity grades based on TG13 as a matter of convenience.
TG13: Tokyo Guidelines 2013 and AC: acute cholecystitis.

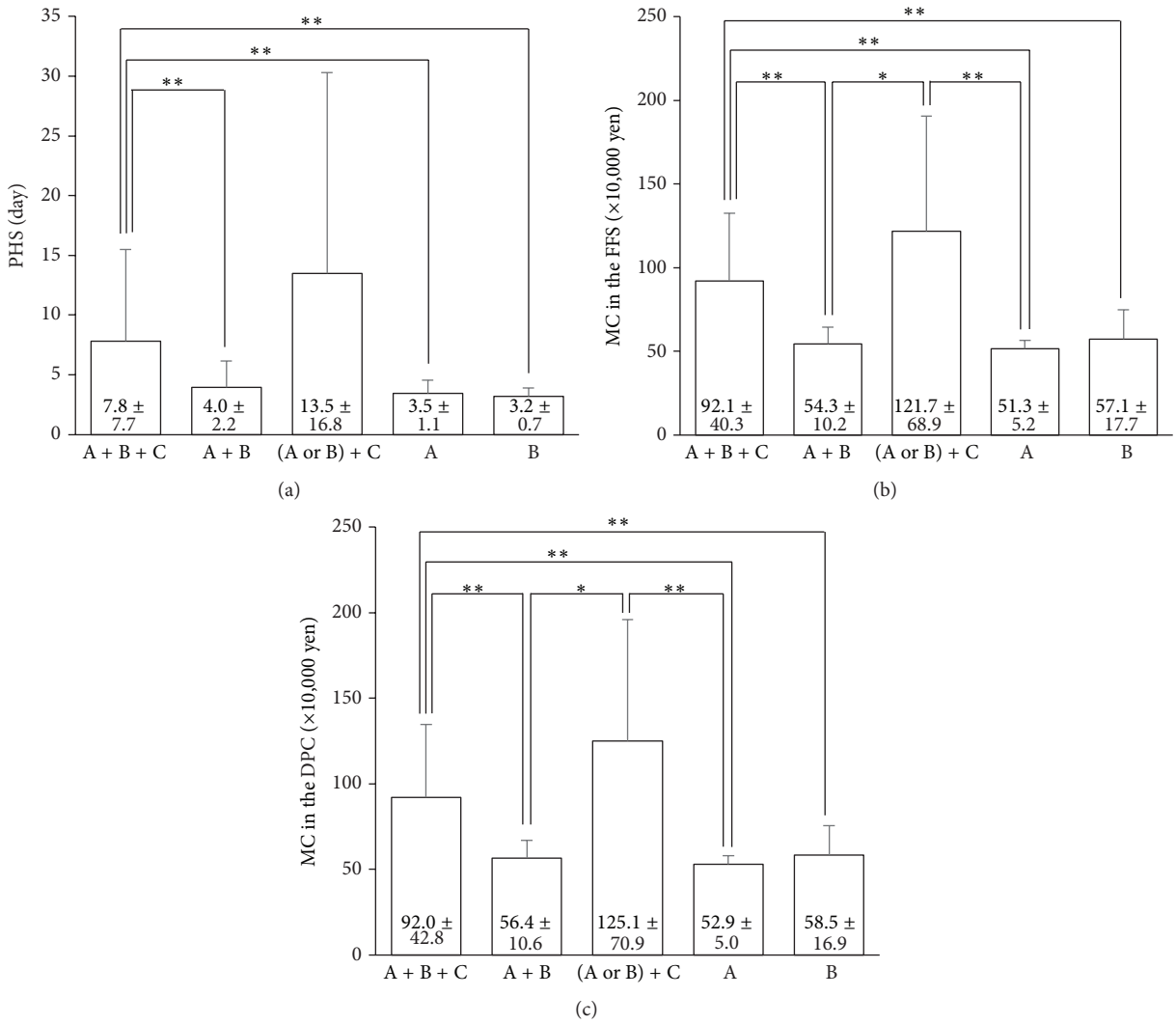

Figure 2: Comparison of PHS and MC in the FFS and DPC systems according to the five groups ($n = 171$). (a) The differences in the average PHS for each group. (b) The differences in the average MC in the FFS system for each group. (c) The differences in the average MC in the DPC system for each group. PHS: postoperative hospital stay, MC: medical costs, FFS: fee for service, and DPC: diagnosis procedure combination. $^{**}P < 0.01$ and $^{*}P < 0.05$.

Table 3: Postoperative complications according to severity grade in the 171 patients who had definite, suspected, or unmatched AC diagnoses.

Complications	Grade I ($n = 139$)	Grade II ($n = 20$)	Grade III ($n = 12$)
Urinary tract infection	0	0	1
Acute cholangitis	0	0	1
Decreased activities of daily living	0	0	3
Surgical site infection	1	1	0
Loss of appetite	1	0	2
Aspiration pneumonia	0	1	0
Deep vein thrombosis	1	0	0
Delirium	0	1	0
Other	2	0	0
Total ($n = 17$)	6 (4.3%)	3 (15.0%)	8 (66.7%)

AC: acute cholecystitis.

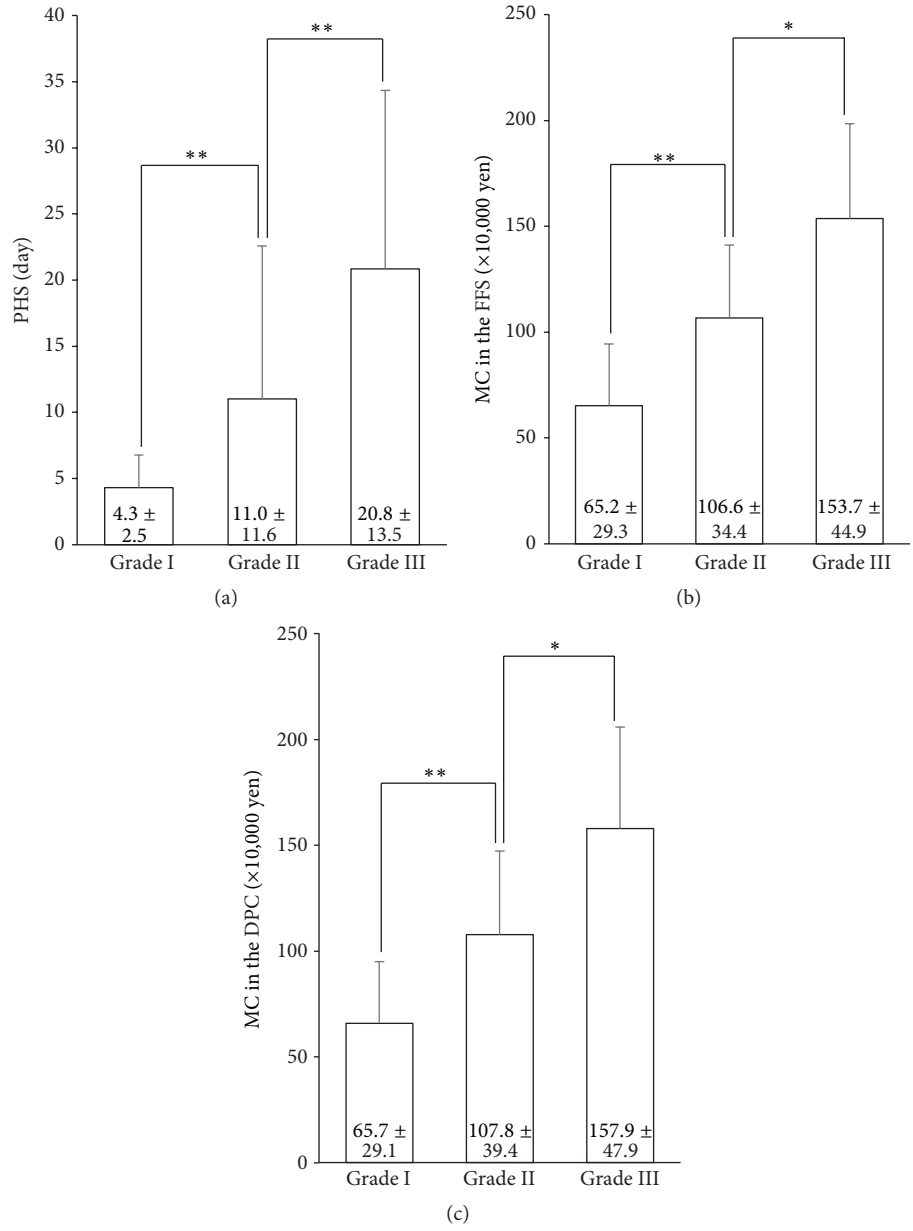

Figure 3: Comparison of PHS and MC according to severity grade ($n = 171$). (a) The differences in the average PHS for each grade. (b) The differences in the average MC in the FFS system for each grade. (c) The differences in the average MC in the DPC system for each grade. PHS: postoperative hospital stay, MC: medical costs, FFS: fee for service, and DPC: diagnosis procedure combination. $^{**}P < 0.01$ and $^{*}P < 0.05$.

There was no postoperative mortality, and the incidence of postoperative complications significantly increased with severity grade: 4.3% in Grade I, 15.0% in Grade II, and 66.7% in Grade III. The incidence of preoperative drainage in Grade III was significantly higher than that in Grade I: 66.7% (8/12) versus 12.1% (15/124) ($P < 0.001$).

When we compared PHS and MC (×10,000 yen) in the FFS and DPC systems according to severity grades based on TG13 (Figure 3), PHS and MC were significantly stratified for each grade. MC in the DPC system was strongly correlated with MC in the FFS system ($R = 0.99$, $P < 0.001$) (Figure 4(a)). Furthermore, we found that PHS was significantly correlated with MC in the FFS system ($R = 0.78$, $P < 0.001$), although some patients had markedly longer or shorter PHS compared to MC (Figure 4(b)). Therefore, we performed univariate and multivariate analyses of preoperative factors influencing PHS and MC.

Univariate analysis revealed the 21 preoperative factors significantly correlated with PHS as shown in Table 4. Interestingly, among three signs of A, B, and C for AC diagnosis, B ($P = 0.004$) and C ($P < 0.001$) were significantly associated with prolonged PHS. Multivariate analysis using these 21 factors identified the three factors of PS, WBC, and severity grade based on TG13 as significant independent

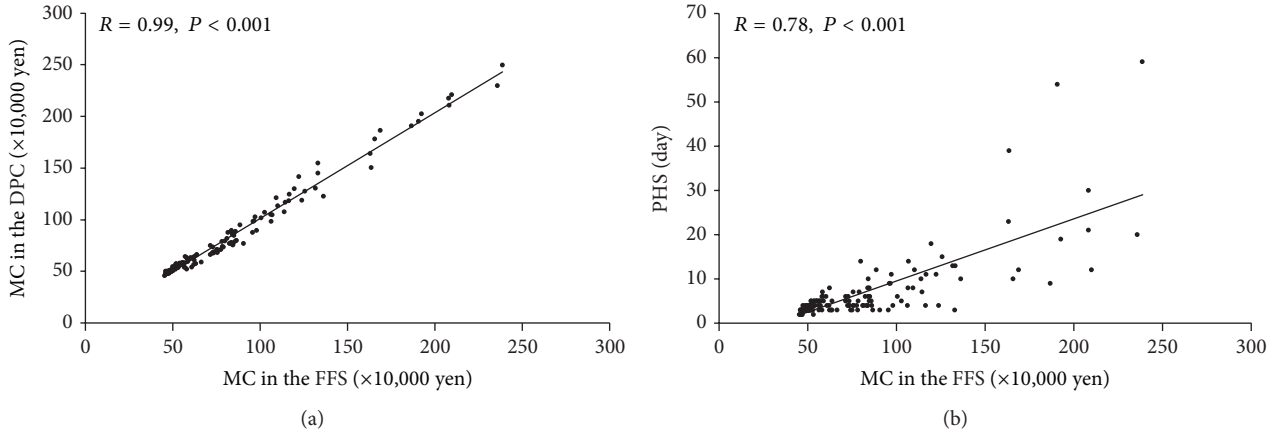

Figure 4: (a) Relationship between MC in the FFS system and MC in the DPC system ($n = 171$). (b) Relationship between PHS and MC in the FFS system ($n = 171$). PHS: postoperative hospital stay, MC: medical costs, FFS: fee for service, and DPC: diagnosis procedure combination.

Table 4: Univariate analyses of the factors influencing PHS in the 171 patients who had definite, suspected, or unmatched AC diagnoses.

Variables	Regression coefficient	P value
Age	0.205	<0.001**
Sex	2.168	0.055
BMI	−0.374	0.025*
DM	1.632	0.325
PS	9.920	<0.001**
Gallbladder stone	−12.911	0.013*
CBD stone	4.472	0.008**
Acute cholangitis	3.199	0.033*
Acute pancreatitis	−2.350	0.381
Preoperative biliary drainage	5.949	<0.001**
Hospital stay before surgery	0.414	<0.001**
Preoperative fasting period	0.679	<0.001**
WBC	0.556	<0.001**
Hb	−1.503	<0.001**
Plt	−0.035	<0.001**
CRP	0.315	<0.001**
Alb	−4.832	<0.001**
BUN	0.244	<0.001**
Cr	1.222	0.110
T-Bil	1.667	<0.001**
AST	0.001	0.544
ALT	0.002	0.523
ALP	0.004	0.018*
γ-GTP	−0.0001	0.947
AMY	0.0000	0.973
PT-INR	19553	<0.001**
Severity grade based on TG13	7.859	<0.001**
A for the diagnosis of AC based on TG13	−2.632	0.143
B for the diagnosis of AC based on TG13	3.707	0.004**
C for the diagnosis of AC based on TG13	4.830	<0.001**

PHS: postoperative hospital stay, AC: acute cholecystitis, BMI: body mass index, DM: diabetes mellitus, PS: performance status, CBD: common bile duct, WBC: white blood cell, Hb: hemoglobin, Plt: platelet cell, CRP: C-reactive protein, Alb: albumin, BUN: blood urea nitrogen, Cr: creatinine, T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase, AMY: serum amylase, and PT-INR: prothrombin time-international normalized ratio. $^{**}P < 0.01$ and $^{*}P < 0.05$.

preoperative factors influencing PHS (Table 5). Regarding MC, univariate analysis revealed the 24 preoperative factors significantly correlated with MC, and multivariate analysis using these 24 factors identified the six factors of age, PS, preoperative biliary drainage, hospital stay before surgery, albumin, and severity grade based on TG13 as significant independent preoperative factors influencing MC (Table 6).

4. Discussion

AC severity grading in TG13 focuses on the presence of organ dysfunction and is considered to predict severity accurately. When AC becomes more severe, it increases the risk of major complications and results in prolonged PHS [3]. However, no reports have evaluated the usefulness of the TG13 severity grading of AC in terms of PHS and MC. Our results showed that PHS and MC were significantly increased in the order of severity grades, although our study included patients with definite, suspected, or unmatched AC diagnoses. In order to reduce MC, DPC was introduced in 2003 in Japan [18]. Recent database analyses comparing the DPC and FFS systems for patients with acute myocardial infarction revealed that the DPC system significantly reduced total accumulated medical charges [32]. In the present study, however, a linear correlation ($R = 0.99$, $P < 0.001$) between MC in the DPC and FFS systems was observed, which in turn demonstrated that the DPC system in this cohort of patients did not reduce MC.

In contrast, the relationship between PHS and MC evaluated by the FFS system did not show a linear correlation, because some patients had markedly longer or shorter PHS compared to MC as shown in Figure 4(b). In order to clarify the significant preoperative factors influencing PHS, we performed univariate and multivariate analyses, which identified three significant independent factors: PS, WBC, and severity grade based on TG13. Cheng et al. assessed the impact of TG13 and the presence of comorbidities on clinical outcomes in 103 patients with AC by univariate and multivariate regression analyses [3]. According to multivariate analysis, patients with

Table 5: Multivariate analyses of the factors influencing PHS in the 171 patients who had definite, suspected, or unmatched AC diagnoses.

Variables	Regression coefficient	P value
Age	0.0579	0.1106
BMI	0.0638	0.6531
PS	4.4929	0.0022**
Gallbladder stone	−2.7409	0.5475
CBD stone	2.1809	0.3002
Acute cholangitis	−1.9900	0.2351
Preoperative biliary drainage	−0.7287	0.6988
Hospital stay before surgery	−0.0768	0.4268
Preoperative fasting period	0.1777	0.2807
WBC	−0.4312	0.0107*
Hb	0.3093	0.4013
Plt	0.0007	0.9304
CRP	−0.0379	0.6538
Alb	−1.8506	0.1447
BUN	0.0855	0.0567
T-Bil	0.4488	0.3045
ALP	−0.0029	0.1186
PT-INR	1.3707	0.7111
Severity grade based on TG13	6.6843	<0.001**
B for the diagnosis of AC based on TG13	0.6840	0.5722
C for the diagnosis of AC based on TG13	1.3101	0.3456

PHS: postoperative hospital stay, AC: acute cholecystitis, BMI: body mass index, PS: performance status, CBD: common bile duct, WBC: white blood cell, Hb: hemoglobin, Plt: platelet cell, CRP: C-reactive protein, Alb: albumin, BUN: blood urea nitrogen, T-Bil: total bilirubin, ALP: alkaline phosphatase, PT-INR: prothrombin time-international normalized ratio, and TG13: Tokyo Guidelines 2013. ** $P < 0.01$ and * $P < 0.05$.

Table 6: Multivariate analyses of the factors influencing MC in the FFS system in the 171 patients who had definite, suspected, or unmatched AC diagnoses.

Variables	Regression coefficient	P value
Age	0.3518	0.0050**
BMI	0.1676	0.7263
PS	19.7213	<0.001**
CBD stone	2.2151	0.7495
Acute cholangitis	−2.7459	0.6357
Preoperative biliary drainage	13.5827	0.0320*
Hospital stay before surgery	2.6646	<0.001**
Preoperative fasting period	0.9821	0.0586
WBC	−0.5084	0.3568
Hb	1.0317	0.4094
Plt	0.0169	0.5015
CRP	−0.0842	0.7555
Alb	−10.1145	0.0197*
BUN	0.0705	0.7116
Cr	1.1566	0.6605
T-Bil	0.4788	0.7585
AST	−0.0126	0.3581
ALT	0.0181	0.3973
ALP	−0.0122	0.0719
γ-GTP	0.0041	0.5503
PT-INR	9.1888	0.4562
Severity grade based on TG13	14.4135	<0.001**
B for the diagnosis of AC based on TG13	−0.8822	0.8311
C for the diagnosis of AC based on TG13	2.1487	0.6437

MC: medical costs, FFS: fee for service, AC: acute cholecystitis, BMI: body mass index, PS: performance status, CBD: common bile duct, WBC: white blood cell, Hb: hemoglobin, Plt: platelet cell, CRP: C-reactive protein, Alb: albumin, BUN: blood urea nitrogen, Cr: creatinine, T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase, PT-INR: prothrombin time-international normalized ratio, and TG13: Tokyo Guidelines 2013. ** $P < 0.01$ and * $P < 0.05$.

Grade III in TG13, higher Charlson's comorbidity scores (assessing the prognostic burden of comorbid disease), and postoperative complications had longer hospital stays. Furthermore, Murata et al. performed a large database analysis using Japanese DPC data in 2176 patients with AC in 2008, and multiple linear regression analyses revealed that early and laparoscopic cholecystectomy was significantly associated with a decrease in length of stay, whereas severity of comorbid conditions, age ≥ 80 years, intensive care unit use, longer pre- and postoperative antimicrobial therapy, and gallbladder drainage were significantly associated with an increase in length of hospital stay [11]. According to these previous studies, preoperative factors influencing length of hospital stay are severity grade based on TG13, severity of comorbid conditions, age, preoperative antimicrobial therapy, and gallbladder drainage. Severity of comorbid conditions including Charlson's comorbidity score, which includes the presence of hemiplegia and dementia, is associated with PS. No reports have evaluated the significance of PS in the length of hospital stay in patients with AC. According to an international prospective study of 460 elderly patients with cancer, PS was significantly associated with extended hospital stay [33]. Interestingly, in the present study, PS was not identified as a significant independent factor predicting PHS when we classified PS 0, 1, and 2 as "better" and PS 3 and 4 as "poor." This indicated that the difference between the patients who were up and about more than 50% of waking hours (PS 3) and those who were confined to bed or a chair more than 50% of waking hours (PS 4) significantly influences PHS. WBC is a significant prognostic factor of AC [2, 34, 35]; therefore, an increased WBC is associated with prolonged PHS.

On the other hand, we revealed that significant independent preoperative factors influencing MC were age, PS, preoperative biliary drainage, hospital stay before surgery, albumin, and severity grade based on TG13. PS and severity grade were identified as significant independent factors influencing PHS and MC. Although we can understand that

preoperative biliary drainage and hospital stay before surgery were associated with increased MC, it is difficult to explain why increased age and decreased albumin were significant independent factors, because there are no previous reports of MC analysis in AC. We speculate that elderly patients require more medical resources including drugs and that decreased albumin levels are associated with poor nutrition, which may increase MC.

With regard to AC diagnostic criteria, our study suggests that imaging findings (C) are essential for diagnosis, because the patients belonging to A + B + C and (A or B) + C were equivalent in PHS and MC, and univariate analysis revealed that B and C ($P < 0.001$) were significantly associated with prolonged PHS. Some patients who are elderly and/or have dementia or paralysis are unlikely to present with local signs of inflammation (A) or systemic signs of inflammation (B) [21] because of their decreased antistress capacity, especially the elderly [22, 23]. In the elderly with AC, the significance of ultrasound examination prior to cholecystectomy is emphasized because ultrasound score can accurately determine AC severity and may be used as a reference for surgical intervention timing and mode selection to guide clinical therapy [24]. Therefore, we recommend reassessment of the TG13 diagnostic criteria by taking the elderly and/or those with dementia into consideration.

5. Conclusions

PS and severity grade based on TG13 significantly influence prolonged PHS as well as increased MC in patients with definite, suspected, or unmatched AC diagnosis, and we have to pay attention to the elderly and those with dementia who may show AC findings on imaging studies but lack local or systemic signs of inflammation.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

References

[1] R. Bittner, "The standard of laparoscopic cholecystectomy," *Langenbeck's Archives of Surgery*, vol. 389, no. 3, pp. 157–163, 2004.

[2] S.-W. Lee, S.-S. Yang, C.-S. Chang, and H.-J. Yeh, "Impact of the Tokyo guidelines on the management of patients with acute calculous cholecystitis," *Journal of Gastroenterology and Hepatology*, vol. 24, no. 12, pp. 1857–1861, 2009.

[3] W.-C. Cheng, Y.-C. Chiu, C.-H. Chuang, and C.-Y. Chen, "Assessing clinical outcomes of patients with acute calculous cholecystitis in addition to the Tokyo grading: a retrospective study," *Kaohsiung Journal of Medical Sciences*, vol. 30, no. 9, pp. 459–465, 2014.

[4] T. Takada, Y. Nimura, K. Hirata, Y. Kawarada, H. Yasuda, Y. Yamashita et al., *Evidence Based Clinical Practice Guidelines for the Management of Acute Cholangitis and Cholecystitis*, Igaku Tosho Shuppan, Tokyo, Japan, 1st edition, 2005.

[5] http://link.springer.com/journal/534/14/1/page/1.

[6] T. Mayumi, K. Someya, H. Ootubo et al., "Progression of Tokyo guidelines and Japanese guidelines for management of acute cholangitis and cholecystitis," *Journal of UOEH*, vol. 35, no. 4, pp. 249–257, 2013.

[7] http://link.springer.com/journal/534/20/1/page/1.

[8] K. Kuwabara, S. Matsuda, K. B. Ishikawa, H. Horiguchi, and K. Fujimori, "Comparative quality of laparoscopic and open cholecystectomy in the elderly using propensity score matching analysis," *Gastroenterology Research and Practice*, vol. 2010, Article ID 490147, 10 pages, 2010.

[9] S. L. Zacks, R. S. Sandler, R. Rutledge, and R. S. Brown Jr., "A population-based cohort study comparing laparoscopic cholecystectomy and open cholecystectomy," *The American Journal of Gastroenterology*, vol. 97, no. 2, pp. 334–340, 2002.

[10] E. B. Bass, H. A. Pitt, and K. D. Lillemoe, "Cost-effectiveness of laparoscopic cholecystectomy versus open cholecystectomy," *The American Journal of Surgery*, vol. 165, no. 4, pp. 466–471, 1993.

[11] A. Murata, K. Okamoto, S. Matsuda et al., "Multivariate analysis of factors influencing length of hospitalization and medical costs of cholecystectomy for acute cholecystitis in Japan: a national database analysis," *Keio Journal of Medicine*, vol. 62, no. 3, pp. 83–94, 2013.

[12] M. Sekimoto, Y. Imanaka, M. Hirose, T. Ishizaki, G. Murakami, and Y. Fukata, "Impact of treatment policies on patient outcomes and resource utilization in acute cholecystitis in Japanese hospitals," *BMC Health Services Research*, vol. 6, article 40, 2006.

[13] A. Brodsky, I. Matter, E. Sabo, A. Cohen, J. Abrahamson, and S. Eldar, "Laparoscopic cholecystectomy for acute cholecystitis: can the need for conversion and the probability of complications be predicted? A prospective study," *Surgical Endoscopy*, vol. 14, no. 8, pp. 755–760, 2000.

[14] J. P. Araujo-Teixeira, J. Rocha-Reis, A. Costa-Cabral, H. Barros, A. C. Saraiva, and A. M. Araujo-Teixeira, "Laparoscopic versus open cholecystectomy for acute cholecystitis (200 cases). Comparison of results and predictive factors for conversion," *Chirurgie*, vol. 124, no. 5, pp. 529–535, 1999.

[15] D. W. Rattner, C. Ferguson, and A. L. Warshaw, "Factors associated with successful laparoscopic cholecystectomy for acute cholecystitis," *Annals of Surgery*, vol. 217, no. 3, pp. 233–236, 1993.

[16] T. Fujii, H. Kato, M. Suzaki, T. Noguchi, and S. Isaji, "Is it possible to predict the development of an incisional surgical site infection and its severity after biliary tract surgery for benign disease?" *Journal of Hepato-Biliary-Pancreatic Sciences*, vol. 19, no. 4, pp. 389–396, 2012.

[17] http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iryouhoken/h26_dpc.html.

[18] Y. Nakagawa, T. Takemura, H. Yoshihara, and Y. Nakagawa, "A new accounting system for financial balance based on personnel cost after the introduction of a DPC/DRG system," *Journal of Medical Systems*, vol. 35, no. 2, pp. 251–264, 2011.

[19] A. Murata, K. Okamoto, S. Matsuda et al., "The care processes for acute cholecystitis according to clinical practice guidelines based on the Japanese administrative database," *Tohoku Journal of Experimental Medicine*, vol. 227, no. 4, pp. 237–244, 2012.

[20] M. Yokoe, T. Takada, S. M. Strasberg et al., "TG13 diagnostic criteria and severity grading of acute cholecystitis (with videos)," *Journal of Hepato-Biliary-Pancreatic Sciences*, vol. 20, no. 1, pp. 35–46, 2013.

[21] A. Meguru, N. Kotaro, E. Naohisa, M. Ryo, A. Mitsuhiko, Y. Takatsugu et al., "A validation study of the updated Tokyo

Guidelines of acute cholesystitis," *Journal of Japan Biliary Association*, vol. 28, pp. 627–632, 2014 (Japanese).

[22] E. A. McGillicuddy, K. M. Schuster, K. Barre et al., "Non-operative management of acute cholecystitis in the elderly," *British Journal of Surgery*, vol. 99, no. 9, pp. 1254–1261, 2012.

[23] M. Li, N. Li, W. Ji et al., "Percutaneous cholecystostomy is a definitive treatment for acute cholecystitis in elderly high-risk patients," *American Surgeon*, vol. 79, no. 5, pp. 524–527, 2013.

[24] L. Zhang, Q. Han, H. Zhang, D. Li, and K. Yao, "Significance and clinical applications of ultrasound score in assessing the clinical severity of acute cholecystitis in the elderly," *Aging Clinical and Experimental Research*, vol. 27, no. 1, pp. 21–26, 2015.

[25] K. A. Meyer, N. J. Capos, and A. I. Mittelpunkt, "Personal experiences with 1,261 cases of acute and chronic cholecystitis and cholelithiasis," *Surgery*, vol. 61, no. 5, pp. 661–668, 1967.

[26] R. A. Gingrich, W. C. Awe, A. M. Boyden, and C. G. Peterson, "Cholecystostomy in acute cholecystitis. Factors influencing morbidity and mortality," *The American Journal of Surgery*, vol. 116, no. 2, pp. 310–315, 1968.

[27] C. Papi, M. Catarci, L. D'Ambrosio et al., "Timing of cholecystectomy for acute calculous cholecystitis: a meta-analysis," *The American Journal of Gastroenterology*, vol. 99, no. 1, pp. 147–155, 2004.

[28] U. Giger, J. M. Michel, R. Vonlanthen, K. Becker, T. Kocher, and L. Krähenbühl, "Laparoscopic cholecystectomy in acute cholecystitis: indication, technique, risk and outcome," *Langenbeck's Archives of Surgery*, vol. 390, no. 5, pp. 373–380, 2005.

[29] G. Borzellino, S. Sauerland, A. M. Minicozzi et al., "Laparoscopic cholecystectomy for severe acute cholecystitis. A meta-analysis of results," *Surgical Endoscopy and Other Interventional Techniques*, vol. 22, no. 1, pp. 8–15, 2008.

[30] An Official Document of Ministry Secretariat of Health and Welfare for the Elderly Bureau, *Criteria for Evaluating the Degree of Independence (Degree of "Bedriddenness") of Disabled Elderly Persons in Performing Activities of Daily Living*, Rohken Publication no. 102-2, An Official Document of Ministry Secretariat of Health and Welfare for the Elderly Bureau, Tokyo, Japan, 1991 (Japanese).

[31] M. M. Oken, R. H. Creech, and T. E. Davis, "Toxicology and response criteria of the Eastern Cooperative Oncology Group," *American Journal of Clinical Oncology: Cancer Clinical Trials*, vol. 5, no. 6, pp. 649–655, 1982.

[32] H. Hamada, M. Sekimoto, and Y. Imanaka, "Effects of the per diem prospective payment system with DRG-like grouping system (DPC/PDPS) on resource usage and healthcare quality in Japan," *Health Policy*, vol. 107, no. 2-3, pp. 194–201, 2012.

[33] R. A. Audisio, D. Pope, H. S. Ramesh et al., "Shall we operate? Preoperative assessment in elderly cancer patients (PACE) can help. A SIOG surgical task force prospective study," *Critical Reviews in Oncology/hematology*, vol. 65, no. 2, pp. 156–163, 2008.

[34] S. P. Fagan, S. S. Awad, K. Rahwan et al., "Prognostic factors for the development of gangrenous cholecystitis," *The American Journal of Surgery*, vol. 186, no. 5, pp. 481–485, 2003.

[35] M. J. Shapiro, W. B. Luchtefeld, S. Kurzweil, D. L. Kaminski, R. M. Durham, and J. E. Mazuski, "Acute acalculous cholecystitis in the critically ill," *American Surgeon*, vol. 60, no. 5, pp. 335–339, 1994.

Hindawi Publishing Corporation
Gastroenterology Research and Practice
Volume 2016, Article ID 3692096, 7 pages
http://dx.doi.org/10.1155/2016/3692096

Research Article

The Hepaticojejunostomy Technique with Intra-Anastomotic Stent in Biliary Diseases and Its Evolution throughout the Years: A Technical Analysis

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Received 21 January 2016; Accepted 28 March 2016

Academic Editor: Alessandro Zerbi

Roux-en-Y hepaticojejunostomy (RYHJ) is currently considered as the definitive treatment for iatrogenic bile duct injuries and the principal representative of biliary diversion procedures. This technique has met many milestones of extensive evolution, particularly the last years of concomitant technological evolution (laparoscopic/robotic approach). Anastomotic strictures and leaks, which may have deleterious effects on the survival and quality of life of a patient with biliary obstruction of any cause, made the need of the development of a safe and efficient RYHJ compulsory. The aim of this technical analysis and the juxtaposed discussions is to elucidate with the most important milestones and technical tips and tricks all aspects of a feasible and reliable RYHJ technique that is performed in our center for the last 25 years in around 400 patients.

1. Introduction

Roux-en-Y hepaticojejunostomy (RYHJ) is currently considered as the definitive treatment for iatrogenic bile duct injuries [1]. It is a common operation, not only to bypass extrahepatic biliary obstructions, but also to establish biliary-enteric continuity after resections for benign and malignant diseases. Studies have shown good medium- and long-term outcomes following this procedure [1, 2]. Postoperative stricture formation at the anastomotic site varies throughout the literature from 4 to 38% of patients [3–5]. Untreated HJ stricture could lead to long-term complications such as choledocholithisis, cholangitis, liver abscess formation, secondary biliary cirrhosis, and portal hypertension [6]. Although revision HJ is required in about 20–25% of patients [7], the majority of such strictures can be treated by dilation via transhepatic or jejunal routes [8]. Indisputable tenets of this procedure include the creation of a durable jejunojejunostomy, followed by the creation of a tension-free anastomosis between the hepatic duct and the defunctionalized jejunal limb.

Anastomotic site stricture is a recognized complication of HJ. Bismuth-Corlette classification type of bile duct injury, revision surgery, nondilated proximal biliary system, and electrocautery damage are implicated in its occurrence [8].

The presence of dilated proximal bile duct is of paramount technical and clinical importance since when the ducts are dilated due to biliary obstruction, the anastomosis could be easy to constitute, which in turn minimizes the risk for postoperative complications but this is not the case in nondilated ducts.

It is a matter of debate among surgeons which operative technique must be chosen in order to prevent the anastomotic failures in cases with small nondilated ducts and whether the selective use of a transanastomotic stent could be of benefit in order to minimize the risk of stricture formation [9].

The aim of this technical analysis and the juxtaposed discussions is to elucidate with the most important milestones and technical tips and tricks all aspects of a feasible and reliable RYHJ technique with intra-anastomotic stenting with low leakage and stricture rates that can be successfully applied

in a variety of biliary diseases; it is to be hoped that some global insights will emerge.

2. Milestones of the Evolution of Biliary Diversion Procedures

The history of biliary diversion procedures began almost a century ago, with the first report of choledochojejunostomy (CJ), the predecessor of hepaticojejunostomy (HJ), made in 1921 by Reid [10] whereas Maingot [11] presented the first case of concomitant cholecystectomy and CJ. The first report with the term hepaticojejunostomy (HJ) was made in the literature in 1949 by Sanders in a case of hemihepatectomy with HJ for irreparable defects of the bile ducts [12]. In 1950, Best introduced the use of T-tube in cases of CJ [13]. In 1952, Corff et al. [14] published the very first series of CJ with cholangiography whereas Allbritten Jr. introduced for the first time the term Roux-en-Y CJ (RYCJ) [15]. 1956 was a year of updates for CJ since 2 novel techniques of CJ were published, the Allen technique [16] and the Warren modification [17].

It was late 70s when the first evaluation of the feasibility and safety of RYHJ in the treatment of benign biliary diseases was published by Bismuth et al. [18] in a retrospective analysis of 123 patients. It was shown that this operation has 0% mortality rate and low learning curve and morbidity rate. The same year, Daugherty et al. [19] announced proximal hepatic duct reconstruction in benign and malignant biliary diseases using sutureless mucosal graft HJ, with all patients presenting with improvement of their symptoms postoperatively. A year later, the experience from Japan on intrahepatic pigment calculi treated with modified wraparound end-to-end HJ was presented to provide an effective and alternative method of treatment [20].

In 1984, Barker and Winkler [21] described a new technique of RYHJ with permanent access by involving the incorporation of a cutaneous access stoma in the Roux-en-Y loop of jejunum used for the anastomosis. This stoma provides permanent access to the anastomosis and to the hepatobiliary tree for nonoperative management of chronic and recurrent biliary tract problems.

In 1987, Bismuth et al. [22] announced the first application of RYHJ in the liver transplant setting as a safe and feasible approach to perform biliary anastomosis. In early 90s, there were the first data of the hedge-up comparison between RYHJ and jejunal interposition hepaticoduodenostomy to treat congenital dilation biliary tract diseases and the former was found superior in terms of postoperative reflux gastritis [23]. At the same period, Quintero et al. [24] published their data on RYHJ with subcutaneous access and the use of Gianturco stents as a method to control recurrent biliary strictures.

In 1998, the first experience of laparoscopic technique RYHJ in experimental setting with the application of transient endoluminally stented anastomosis (TESA) was announced [25]. This approach gave birth to the evolution of intra-anastomotic stenting and the laparoscopic approach when performing RYHJ.

At the end of the previous century, 2 technical advances of RYHJ were published. The first was a new technique of Hepp-Couinaud HJ using the posterior approach to the hepatic hilum, approach that was proven safe and feasible despite being evaluated as a case report [26], and the second was the first case controlled study evaluating the role and efficacy of laparoscopic RYHJ as a palliative treatment in the clinical setting of pancreatic cancer [27]. The results were encouraging in terms of mortality, morbidity, and length of hospitalization. In all categories, the laparoscopic approach was found superior compared to open RYHJ.

In 2002, Nagino et al. [28] developed new placement of RY jejunal limb in which the limb is placed via the retrocolic-retrogastric route in 133 consecutive obese patients and achieved tension-free anastomosis in all patients with neither early nor late complications directly related to this new reconstruction route occurring.

In 2004, the first robotically assisted laparoscopic RYHJ was performed in experimental setting and a feasibility study between the latter and pure laparoscopic and open approach took place [29]. The procedure was found feasible and safe but more time-consuming than the open approach. In the same year, the application of an external metallic circle instead of intra-anastomotic stent in low caliber anastomoses in the setting of RYHJ was suggested [30].

Three years later, in the clinical setting, a robotically assisted complete excision of choledochal cyst type I and concomitant extracorporeal RYHJ was performed [31]. The approach was compared with current literature standards on the treatment of choledochal cyst type I and was found noninferior compared to laparoscopic setup. In 2012, the first single-incision laparoscopic RYHJ was performed using conventional instruments in children with choledochal cysts offering noninferior postoperative results in terms of length of hospital stay and time to feed compared to conventional laparoscopic approach [32].

Nowadays, the intermediate-term outcome for totally laparoscopic choledochal cyst excision and RYHJ at a single center in a 5-year period was published and concluded that this procedure is a safe and efficacious procedure for the most instances of adult choledochal cyst demanding advanced laparoscopic skills, good team cooperation, and stapler anastomosis [33].

Table 1 summarizes the crucial milestones of the evolution of the biliary diversion operations throughout the years.

3. Our RYHJ Technique

Herein, we describe a step-by-step analysis of our technique as we use it during the last 25 years in more than 400 patients. After careful dissection and division of the extrahepatic, hilar, or intrahepatic bile duct(s) (depends on the operation indication), the arterial blood supply of the proximal cutting edge is checked. In cases of insufficient bleeding from the bile duct stump(s), the preparation is continued cranially, until satisfactory arterial bleeding is observed. Neighboring bile ducts with a small orifice diameter were transformed into a common channel, using one to two PDS 5-0 or 6-0 (PDS®; Ethicon, Hamburg, Germany) interrupted stitches. In order to achieve sufficient bile duct caliber we prefer to open up the left hepatic duct but keeping the posterior wall of the

Table 1: Milestones of the evolution of biliary diversion techniques.

Author	Year	Technique	Novelty
Reid [10]	1921	CJ	First report of the technique
Sanders [12]	1949	HJ	First report of the technique
Allbritten Jr. [15]	1953	RYCJ	First report of the technique
Allen [16] and Warren [17]	1956	CJ	Introduction of a modified CJ technique
Bismuth et al. [18]	1978	RYHJ	Feasibility and safety study
Bismuth et al. [22]	1987	RYHJ	First application in liver transplantation
Röthlin et al. [7]	1998	Lap RYHJ	First retrospective analysis on the safety and feasibility
Nagino et al. [28]	2002	RYHJ	Limb placed via the retrocolic-retrogastric route in obese patients
Kang et al. [31]	2007	Robotic-assisted RYHJ	First experience in clinical setting
Diao et al. [32]	2012	SILS RYHJ	Performed using conventional instruments in children with choledochal cysts

bifurcation, according to the Hepp-Couinaud technique [34]. In case that the stenosis is covered by liver tissue at the liver hilum, the liver tissue has to be removed using ultrasonic dissection (MISONIX, USA). When there is concomitant vascular injury to the hepatic hilum, we try to avoid early reconstruction after the injury, in order to allow arterial supply regeneration. Stay sutures are placed at the anterior surface and at the 2 corners (3 and 9 hours) in order to improve lumen visibility.

The Roux-en-Y jejunal limb is then prepared by transecting the jejunum around 20–30 cm distal from the Treitz ligament. The stapler-line of the Roux-limb is reinforced with interrupted PDS 4-0 sutures and then brought in a retrocolic (anteduodenal, in the cases where the duodenum is present) fashion, right of the middle colic vessels, to the right upper abdomen. Care must be taken to ensure a tension-free jejunal limb with sufficient length.

A small orifice (5 mm) at the antimesenteric side of the Roux-limb and 2-3 cm distal to stapled jejunal stump is created. When a pancreatoduodenectomy is performed, we prefer to leave a distance of 8–10 cm between the pancreaticojejunostomy and the hepaticojejunostomy. The diameter of the jejunal orifice should always be much smaller than the width of the hepatic duct. The mucosa of the intestinal orifice is slightly inverted, using four PDS 5-0 interrupted stitches in a "crosswise" fashion, in order to create a mucosa-to-mucosa anastomosis (Figure 1). The reason for this step is to ensure a well-adapted duct-to-mucosa HJ.

For the construction of our single-layer, end-to-side HJ we use 4-0 to 6-0 PDS interrupted sutures. The first two sutures are placed in the left corner of the jejunum and the bile duct. The needles are passed through the bile duct from outward to the inside and then through the jejunum from the inside outwards. The jejunal limb is then gently pushed down to the hepatic duct and the sutures are tied. All the passings of the stiches take a good amount of seromuscular part of the small bowel *but not* the mucosa, helping the mucosa to be inside the bile duct and so to complete a mucosa-to-mucosa anastomosis. Besides, we have to mention that every bite to the bile duct has to take a good tissue amount, which has to be at least 4-5 mm in order to avoid tearing and ischemia. The number of stiches we use is related to the caliber of the bile duct and long experience showed us that every step to next stich has to be also 4-5 mm. This number comes mainly from experience but can be also helpful to calculate the number of stiches or bites you are going to use for the whole anastomosis based on the perimeter of the duct (Figure 1).

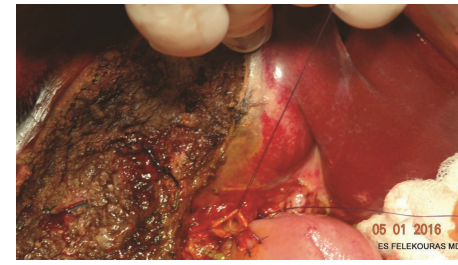

Figure 1: Dissection and division of the extrahepatic bile duct to the level of the biliary confluence of the right and left hepatic ducts at the hilum. Stay sutures with atraumatic needle placed in the stumps of each hepatic duct. The mucosa of the jejunal limb orifice is slightly inverted, using four PDS 5-0 interrupted sutures. Note that the circumference of the duct is $2\pi r = 21.997$, so the bites have to be $2\pi r/4 = 21.997/4 = 5{,}4$ mm. So this anastomosis can be done with 6 stiches (assuming you put your stiches with a step of 4 mm).

The posterior wall of the anastomosis is completed by placing the appropriate number of sutures in the same way from the left to the right. All knots of the posterior wall remain outside of the anastomosis (Figure 2). Attention has to be paid not to tear the bile duct during the ligation. In selected cases, where the bile duct diameter and its wall thickness are big enough, this step can also be done in a "running" fashion.

At this point, we prefer to place a transanastomotic (in-in) stent in order to protect and improve the patency of the anastomosis in the early postoperative period. We usually use an 8-10 French Nelaton catheter or the edge of a 6 Fr. "pigtail" catheter in cases of small bile ducts. The stent is temporarily fixed in place using a 5-0 Vicryl suture (Figure 3). When a PTBD is placed preoperatively, the drainage is preserved and placed intraluminally as an external-internal stent.

The anterior wall of the anastomosis is constructed in the same fashion. Suturing should start from the left to the right side, passing the needle through the jejunum outside-inwards and then through the bile duct from the inside to outward. The sutures are then tied, while the inverted mucosa of the

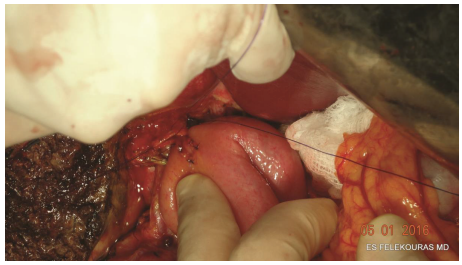

Figure 2: Construction of the posterior wall of the anastomosis. The jejunal limb is gently pushed down to the hepatic duct and the sutures are tied with the knots lying on the outside of the anastomosis.

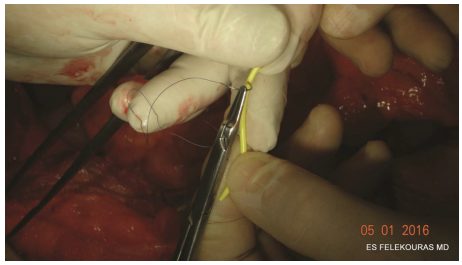

Figure 3: Fixation of the pigtail catheter to the jejunal stump using a 5-0 Vicryl suture.

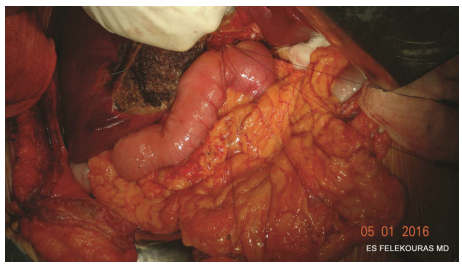

Figure 4: Anterior row of sutures placed to complete the approximation of the jejunum and bile duct.

jejunum should be buried intraluminally (Figure 4). A small trick to achieve that is to bring the knot of the tie on the bowel site.

After the completion of the anastomosis, control for bile leaks (if present) should be performed (Figure 5). When a PTBD is in place, a "white-test" with propofol or lipiodol can be made in order to check the patency and the integrity of the anastomosis. The mean operative time of the technique is 74 minutes.

We strongly believe that the key-points to the long-lasting results of this technique are the prevention of ischemia, the avoidance of bile leak, and the mucosa-to-mucosa anastomosis.

Despite not being the purpose of our analysis, we will briefly report the outcomes of the application of this technique from 1992 till 2015. During this period, 412 patients underwent biliary diversion with the technique described above. The majority of cases were due to pancreatic or

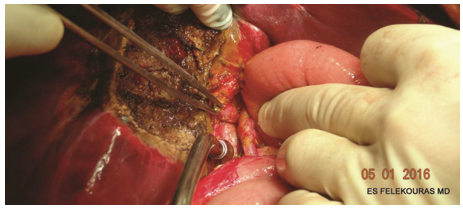

Figure 5: Completion of the hepaticojejunostomy.

ampullary cancer (29%). Around 25% of the cases were BDIs and 12% of the cases were cholangiocarcinomas. Benign biliary (choledochal cyst, choledocholithiasis, etc.) and pancreatic diseases (chronic and autoimmune pancreatitis) reached almost 22% of the cases. Finally, 50 cases (12%) were performed in liver transplantation setting. The number of anastomotic leaks was 8 (2.1%) and the cases of anastomotic strictures reached 12 (3.1%). Other complications included wound infection (38-10%), biloma (9-2.3%), recurrent cholangitis (11-2.88%), biliary peritonitis (2-0.5%), and others (pulmonary embolism, urinary tract infection, pneumonia, etc./13 cases; 3.4%). The overall morbidity rate was 28.2%. The mortality rate reached 3.9% (15 cases). The majority (12/15-80%) of these patients underwent RYHJ in emergency setting.

4. Discussion

The creation of a secure HJ is an essential skill for any hepatobiliary surgeon. And if we take into consideration that an imperfect anastomosis or its failure may lead to reoperations or reinterventions in a patient with recurrent devastating symptoms, the need for well-performed HJ is imperative.

To date, many techniques and approaches have been described. Recently Sutherland and Dixon [35] described a refined technique of sewing the end of the common hepatic duct to the side of the jejunum. The sutures are placed to include all layers of the bowel wall except mucosa. This extramucosal HJ was performed in 185 cases with 1.7% leak rate, a stricture rate of 4.9%, and no mortality [35].

Laukkarinen et al. [36] demonstrated a RYHJ with a transanastomotic biodegradable stent with low rates of anastomotic leakage or stricture in experimental models. The presence of a stent seems to increase the caliber of the anastomosis since postoperative duct diameter was found larger than the preoperative one [36]. Long-term clinical studies are required to confirm these initial experimental findings.

One of the long-standing tenets when performing biliary reconstruction is the use a long hepatic limb to decrease the risk for postoperative cholangitis. Most authors recommend Roux-limbs of up to 75 cm; Felder et al. [37] have routinely used a Roux length of 20 cm to facilitate possible postoperative endoscopic access. In their series they presented less than 6% of anastomotic stricture and 10% of long-term and 3% of immediate complications; most of them required reoperation [37]. We must highlight that almost half of the cases in the series were liver transplantation cases.

Emerging data come from the evaluation of minimal invasive approaches to perform HJ, even in severe BDI injuries. In the laparoscopic setting, it was recently showed that laparoscopic approach to BDI repair is feasible and safe with low morbidity rates (bile leak, 17.2%, reintervention, 6.8%) accompanied with the well-established advantages of laparoscopic surgery (low pain, earlier mobilization, and cosmesis) [38]. In the setting of malignancies, the results are not that satisfactory since the morbidity rate reached 33.3% and mortality was 2.08% in a series of laparoscopic HJ cases for palliative treatment of pancreatic head malignancy [39]. The disadvantages of these series were the short follow-up and the inadequate number of cases. Moreover, it was recently published that E2 BDI injury was successfully treated with robotic-assisted RYHJ [40]. Despite the satisfactory results, this approach is still in its infancy with several disadvantages including the bulky hardware which makes it impossible for the robot to be moved to other theatres, the high learning curve, and the high operating and maintenance cost making it a "forbidden fruit" in the era of financial crisis. The comparison among different technical modalities of performing RYHJ is not always feasible since the indications, the selection of patients, and the surgical experience differ among studies. And although the technique can be meticulously followed, the experience of the surgeon involved in the performance of the anastomosis is the most important issue.

In our institution, we follow a strict evaluation algorithm to each patient referred to us with biliary disease. The postoperative outcomes of our technique are evaluated as categories of wound infection, bile leak, biloma, and biliary peritonitis. The long-term postoperative complications were evaluated as categories of stricture, recurrent cholangitis, defined as the occurrence of two episodes of cholangitis, the need for nonsurgical intervention/dilation (percutaneous drainage of biloma, ERCP and sphincterotomy, and dilation of anastomosis), and the need for reoperation. As we have previously demonstrated, the long-term postoperative morbidity rate of our technique in BDI cases is 26.8% with half of these cases presenting with stricture of the anastomosis with no difference between the early and late intervention group. No patient required reoperation for BDI-related HJ [41]. This rate of anastomotic stricture is noninferior compared to current literature standards and seems rather attractive if one takes into consideration selection bias secondary to the referral pattern [42–44].

Far beyond the surgical stress that an open surgical intervention releases, HJ itself seems to cause many interesting pathophysiological changes. In an animal model it was well described that HJ was associated with less weight gain and colonization of the bile duct with aerobic bacteria, *Escherichia coli*, dominating with concomitant fibrous periportal infiltration [45]. These changes are of potential clinical importance since many of the postoperative complications could be explained to the bactibilia that might be an important factor in the pathogenesis of cholangitis, gallstone formation, and gallstone pancreatitis.

Long-term outcomes in biliary reconstruction are mainly influenced by the level of injury, presence of local inflammation, timing of final repair, type of reconstruction, and experience and expertise of surgeon in these operations and previous attempts of repair in the same or in other institutions. Patients without history of previous interventions, lack of inflammation, lack of complete transection of common bile duct, and greater diameter of bile duct present better operative results, decreased rates of morbidity and mortality, and lower rates of postoperative complications [46, 47].

It is widely accepted that the best results in biliary reconstruction can be achieved in specialized hepatobiliary centers [48]. Nevertheless, many general surgeons without previous experience attempt to repair these injuries, often without proper understanding or characterization of the biliary injury. This may be associated with inferior short-term and long-term outcomes, substantial morbidity, and higher rates of complications [49]. Every failed attempt at repair leads to a decreased bile duct length, making definitive reconstruction more difficult.

5. Conclusions

The RYHJ is a reliable and efficient technique of biliary diversion in most cases of biliary obstruction. It has been significantly developed in the last 100 years till our current era of minimally invasive surgery. We analyze by step-by-step approach the RYHJ technique that we perform in our center. It is established to be a feasible approach, with short learning curve, low anastomotic stricture rates, and almost zero anastomotic leakage cases. It can be applied in a variety of diseases and conditions.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

Demetrios Moris and Evangelos Felekouras designed the study; Demetrios Moris, Alexandros Papalampros, Michail Vailas, and Athanasios Petrou analyzed the data; Michael Kontos and Evangelos Felekouras drafted the paper; Demetrios Moris, Alexandros Papalampros, and Michail Vailas wrote the paper; and Evangelos Felekouras supervised the paper. Demetrios Moris and Alexandros Papalampros equally contributed.

References

[1] K. D. Lillemoe, S. A. Martin, J. L. Cameron et al., "Major bile duct injuries during laparoscopic cholecystectomy. Follow-up after combined surgical and radiologic management," *Annals of Surgery*, vol. 225, no. 5, pp. 459–471, 1997.

[2] K. D. Lillemoe, G. B. Melton, J. L. Cameron et al., "Postoperative bile duct strictures: management and outcome in the 1990s," *Annals of Surgery*, vol. 232, no. 3, pp. 430–441, 2000.

[3] L. Stewart and L. W. Way, "Bile duct injuries during laparoscopic cholecystectomy. Factors that influence the results of treatment," *Archives of Surgery*, vol. 130, no. 10, pp. 1123–1129, 1995.

[4] P. H. Davids, A. K. Tanka, E. A. Rauws et al., "Benign biliary strictures. Surgery or endoscopy?" *Annals of Surgery*, vol. 217, no. 3, pp. 237–243, 1993.

[5] S. R. Johnson, A. Koehler, L. K. Pennington, and D. W. Hanto, "Long-term results of surgical repair of bile duct injuries following laparoscopic cholecystectomy," *Surgery*, vol. 128, no. 4, pp. 668–677, 2000.

[6] L. H. Blumgart, C. J. Kelley, and I. S. Benjamin, "Benign bile duct stricture following cholecystectomy: critical factors in management," *British Journal of Surgery*, vol. 71, no. 11, pp. 836–843, 1984.

[7] M. A. Röthlin, M. Löpfe, R. Schlumpf, and F. Largiadèr, "Long-term results of hepaticojejunostomy for benign lesions of the bile ducts," *The American Journal of Surgery*, vol. 175, no. 1, pp. 22–26, 1998.

[8] R. Al-Ghnaniem and I. S. Benjamin, "Long-term outcome of hepaticojejunostomy with routine access loop formation following iatrogenic bile duct injury," *British Journal of Surgery*, vol. 89, no. 9, pp. 1118–1124, 2002.

[9] M. A. Mercado, C. Chan, H. Orozco et al., "To stent or not to stent bilioenteric anastomosis after iatrogenic injury: a dilemma not answered?" *Archives of Surgery*, vol. 137, no. 1, pp. 60–63, 2002.

[10] M. R. Reid, "Drainage of the common bile duct through the cystic duct," *Annals of Surgery*, vol. 73, no. 4, pp. 458–469, 1921.

[11] R. Maingot, "A plea for cholecystectomy combined with choledochostomy in cases of chronic cholecystitis associated with gall-stones," *Postgraduate Medical Journal*, vol. 13, no. 142, pp. 278–283, 1937.

[12] R. L. Sanders, "Hemihepatectomy with hepaticojejunostomy for irreparable defects of the bile ducts," *Archives of Surgery*, vol. 58, no. 6, pp. 752–761, 1949.

[13] R. R. Best, "Choledochostomy; advantages of a modified T tube," *Surgery, Gynecology & Obstetrics*, vol. 90, no. 3, pp. 295–297, 1950.

[14] M. Corff, S. Berger, and J. Gershon-Cohen, "Choledochostomy with cholangiography; a review of 50 cases," *Surgery, Gynecology & Obstetrics*, vol. 94, no. 4, pp. 394–400, 1952.

[15] F. F. Allbritten Jr., "Recurring pancreatitis and associated stenosis of the common bile duct; treatment by Roux-Y choledochojejunostomy," *AMA Archives of Surgery*, vol. 67, no. 6, pp. 779–789, 1953.

[16] A. W. Allen, "A technique of choledochostomy," *AMA Archives of Surgery*, vol. 72, no. 3, pp. 532–543, 1956.

[17] K. W. Warren, "Technique of cholecystectomy and choledochostomy," *The Surgical Clinics of North America*, vol. 36, no. 3, pp. 687–697, 1956.

[18] H. Bismuth, D. Franco, M. B. Corlette, and J. Hepp, "Long term results of Roux-en-Y hepaticojejunostomy," *Surgery, Gynecology & Obstetrics*, vol. 146, no. 2, pp. 161–167, 1978.

[19] M. Daugherty, C. B. Ernst, C. R. Sachatello, and W. O. Griffen, "Proximal hepatic duct reconstruction. Repair using sutureless mucosal graft hepaticojejunostomy," *Archives of Surgery*, vol. 113, no. 4, pp. 490–495, 1978.

[20] S. Nagamitsu, Y. Mohtai, Y. Maeda, and Y. Kuroda, "Wrap-around end-to-end hepaticojejunostomy (roux-en-Y) for intrahepatic pigment calculi," *The Japanese Journal of Surgery*, vol. 9, no. 1, pp. 49–54, 1979.

[21] E. M. Barker and M. Winkler, "Permanent-access hepaticojejunostomy," *British Journal of Surgery*, vol. 71, no. 3, pp. 188–191, 1984.

[22] H. Bismuth, D. Castaing, J. Gugenheim, O. Traynor, and M. Ciardullo, "Roux-en-Y hepaticojejunostomy: a safe procedure for biliary anastomosis in liver transplantation," *Transplantation Proceedings*, vol. 19, no. 1, pp. 2413–2415, 1987.

[23] A. Okada, J. Higaki, T. Nakamura, and S. Kamata, "Roux-en-Y versus interposition biliary reconstruction," *Surgery Gynecology and Obstetrics*, vol. 174, no. 4, pp. 313–316, 1992.

[24] G. A. Quintero, H. Espinosa, G. Pineres et al., "Roux-en-Y hepaticojejunostomy with subcutaneous access and the use of gianturco stents for the management of biliary tract strictures," *World Journal of Surgery*, vol. 16, no. 6, pp. 1178–1181, 1992.

[25] D. Inderbitzin, R. A. Schmid, F. H. Hetzer, K. A. Zucker, and O. M. Schöb, "Is growth influencing diameter and function of laparoscopic TESA hepaticojejunostomy? A comparison of adult minipigs and juvenile domestic swine," *Journal of Investigative Surgery*, vol. 11, no. 2, pp. 115–122, 1998.

[26] B. Launois, F. R. Sutherland, and H. Harissis, "A new technique of Hepp-Couinaud hepaticojejunostomy using the posterior approach to the hepatic hilum," *Journal of the American College of Surgeons*, vol. 188, no. 1, pp. 59–62, 1999.

[27] M. A. Röthlin, O. Schob, and M. Weber, "Laparoscopic gastro- and hepaticojejunostomy for palliation of pancreatic cancer: a case controlled study," *Surgical Endoscopy*, vol. 13, no. 11, pp. 1065–1069, 1999.

[28] M. Nagino, J. Kamiya, M. Kanai et al., "Hepaticojejunostomy using a Roux-en-Y jejunal limb via the retrocolic-retrogastric route," *Langenbeck's Archives of Surgery*, vol. 387, no. 3-4, pp. 188–189, 2002.

[29] L. Villegas, S. Lagoo, T. Schwartz, N. Athar, R. Greene, and W. S. Eubanks, "Robotically assisted laparoscopic Roux-en-Y hepaticojejunostomy," *JSLS*, vol. 8, no. 3, pp. 239–244, 2004.

[30] E. Gocmen, M. Keskek, M. Tez, S. Karamursel, M. Koc, and M. Kilic, "External metallic circle in hepaticojejunostomy," *BMC Surgery*, vol. 4, article 14, 2004.

[31] C. M. Kang, H. S. Chi, J. Y. Kim et al., "A case of robot-assisted excision of choledochal cyst, hepaticojejunostomy, and extracorporeal Roux-en-y anastomosis using the da Vinci surgical system," *Surgical Laparoscopy, Endoscopy & Percutaneous Techniques*, vol. 17, no. 6, pp. 538–541, 2007.

[32] M. Diao, L. Li, N. Dong, Q. Li, and W. Cheng, "Single-incision laparoscopic Roux-en-Y hepaticojejunostomy using conventional instruments for children with choledochal cysts," *Surgical Endoscopy*, vol. 26, no. 6, pp. 1784–1790, 2012.

[33] X. Duan, X. Mao, B. Jiang, and J. Wu, "Totally laparoscopic cyst excision and roux-en-y hepaticojejunostomy for choledochal cyst in adults: a single-institute experience of 5 years," *Surgical Laparoscopy, Endoscopy and Percutaneous Techniques*, vol. 25, no. 2, pp. e65–e68, 2015.

[34] J. A. Myburgh, "The Hepp-Couinaud approach to strictures of the bile ducts: I. Injuries, choledochal cysts, and pancreatitis," *Annals of Surgery*, vol. 218, no. 5, pp. 615–620, 1993.

[35] F. Sutherland and E. Dixon, "Extramucosal hepaticojejunostomy," *American Journal of Surgery*, vol. 189, no. 6, pp. 667–669, 2005.

[36] J. Laukkarinen, J. Sand, J. Leppiniemi, M. Kellomäki, and I. Nordback, "A novel technique for hepaticojejunostomy for non-dilated bile ducts: a purse-string anastomosis with an intra-anastomotic biodegradable biliary stent," *The American Journal of Surgery*, vol. 200, no. 1, pp. 124–130, 2010.

[37] S. I. Felder, V. G. Menon, N. N. Nissen, D. R. Margulies, S. Lo, and S. D. Colquhoun, "Hepaticojejunostomy using short-limb

Roux-en-Y reconstruction," *JAMA Surgery*, vol. 148, no. 3, pp. 253–258, 2013.

[38] A. Cuendis-Velazquez, C. Morales-Chavez, I. Aguirre-Olmedo et al., "Laparoscopic hepaticojejunostomy after bile duct injury," *Surgical Endoscopy*, vol. 30, no. 3, pp. 876–882, 2016.

[39] G. Kohan, C. G. Ocampo, H. I. Zandalazini et al., "Laparoscopic hepaticojejunostomy and gastrojejunostomy for palliative treatment of pancreatic head cancer in 48 patients," *Surgical Endoscopy and Other Interventional Techniques*, vol. 29, no. 7, pp. 1970–1975, 2015.

[40] A. Prasad, S. De, P. Mishra, and A. Tiwari, "Robotic assisted Roux-en-Y hepaticojejunostomy in a post-cholecystectomy type E2 bile duct injury," *World Journal of Gastroenterology*, vol. 21, no. 6, pp. 1703–1706, 2015.

[41] E. Felekouras, A. Petrou, K. Neofytou et al., "Early or delayed intervention for bile duct injuries following laparoscopic cholecystectomy? A dilemma looking for an answer," *Gastroenterology Research and Practice*, vol. 2015, Article ID 104235, 10 pages, 2015.

[42] J. A. S. B. Jayasundara, W. M. M. de Silva, and A. A. Pathirana, "Therapeutic value and outcome of gastric access loops created during hepaticojejunostomy for iatrogenic bile duct injuries," *Surgeon*, vol. 8, no. 6, pp. 325–329, 2010.

[43] Y. Goykhman, I. Kory, R. Small et al., "Long-term outcome and risk factors of failure after bile duct injury repair," *Journal of Gastrointestinal Surgery*, vol. 12, no. 8, pp. 1412–1417, 2008.

[44] D. Antolovic, M. Koch, L. Galindo et al., "Hepaticojejunostomy—analysis of risk factors for postoperative bile leaks and surgical complications," *Journal of Gastrointestinal Surgery*, vol. 11, no. 5, pp. 555–561, 2007.

[45] J. Laukkarinen, P. Chow, J. Sand et al., "Long-term changes in hepatobiliary physiology after Roux-en-Y hepaticojejunostomy," *The Journal of Surgical Research*, vol. 143, no. 2, pp. 270–275, 2007.

[46] T. Diamantis, C. Tsigris, A. Kiriakopoulos et al., "Bile duct injuries associated with laparoscopic and open cholecystectomy: an 11-year experience in one institute," *Surgery Today*, vol. 35, no. 10, pp. 841–845, 2005.

[47] M. A. Mercado, B. Franssen, I. Dominguez et al., "Transition from a low: to a high-volume centre for bile duct repair: changes in technique and improved outcome," *HPB*, vol. 13, no. 11, pp. 767–773, 2011.

[48] M. A. Hamad, A. A. Nada, M. Y. Abdel-Atty, and A. S. Kawashti, "Major biliary complications in 2,714 cases of laparoscopic cholecystectomy without intraoperative cholangiography: a multicenter retrospective study," *Surgical Endoscopy*, vol. 25, no. 12, pp. 3747–3751, 2011.

[49] C. R. Berney, "Major common bile duct injury and risk of litigation: a surgeon's perspective," *The American Journal of Surgery*, vol. 204, no. 5, pp. 800–802, 2012.

Hindawi Publishing Corporation
Gastroenterology Research and Practice
Volume 2016, Article ID 9381759, 8 pages
http://dx.doi.org/10.1155/2016/9381759

Research Article

Different Types of Periampullary Duodenal Diverticula Are Associated with Occurrence and Recurrence of Bile Duct Stones: A Case-Control Study from a Chinese Center

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Received 3 January 2016; Accepted 8 March 2016

Academic Editor: Pedram Heidari

Aims. We here investigated the association of different types of periampullary diverticula (PAD) with pancreaticobiliary disease and with technical success of endoscopic retrograde cholangiopancreatography (ERCP). *Methods*. A total of 850 consecutive patients who underwent their first ERCP were entered into a database. Of these patients, 161 patients (18.9%) had PAD and the age- and sex-matched control group comprised 483 patients. *Results*. PAD was correlated with common bile duct (CBD) stones (59.6% versus 35.0% in controls; $P = 0.008$) and negatively correlated with periampullary malignancy (6.8% versus 21.5% in controls; $P = 0.004$). The acute pancreatitis was more frequent (62.5%) in patients with PAD type 1 followed by PAD type 2 (28.9%, $P = 0.017$) and type 3 (28.0%, $P = 0.006$). No significant differences were observed in successful cannulation rate and post-ERCP complications among the 3 types of PAD. Type 1 PAD patients had less recurrence of CBD stones than did the patients who had type 2 or type 3 PAD (53.8% versus 85.7%; $P = 0.043$). *Conclusions*. PAD, especially type 1 PAD, is associated with an increased acute pancreatitis as well as occurrence and recurrence of CBD stones. PAD during an ERCP should not be considered as an obstacle to a successful cannulation.

1. Introduction

Periampullary diverticula (PAD), also known as perivaterian or peripapillary diverticula, is extraluminal mucosal outpouching of the duodenal arising within a radius of 2-3 cm from the ampulla of Vater [1]. PAD are observed in around 10–20% of patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) [2] and their incidence increases with age. There are three types of PAD according to the position of the major papilla (inside, adjacent, or outside of the diverticula) in ERCP examination, which have become generally accepted for the classification of PAD [3]. The clinical importance of PAD originates from its association with pancreaticobiliary disease. Several studies have suggested that PAD is the reason for some clinical conditions, such as choledolithiasis and pancreatic disorders [1, 2]. However, the clinical characteristics associated with different types of PAD have not been well investigated. Therefore, we conducted this observational study to investigate the association of different types of PAD with occurrent and recurrent bile duct stones, with pancreatitis, and with the technical success of ERCP.

2. Methods

2.1. Patients. The study included 850 consecutive patients who underwent their first ERCP during the period from August 2008 until December 2012. ERCP was performed when the imaging study and laboratory tests indicated that therapeutic management was needed or the diagnosis was uncertain.

Demographic characteristics, clinical information, imaging studies, and technical details and findings from an ERCP regarding those patients were entered into a database.

After completion of database entry for each patient with PAD, matched cases were selected into the non-PAD group (control group) that had corresponding parameters for age and gender. We adopted a 1 : 3 ratio of case: control proportion

among the 850 consecutive patients who underwent ERCP during the study period. Of these, 161 patients (18.9%) had diverticula and the age- and sex-matched control group comprised 483 patients. This study was approved by the institutional review board of the hospital and informed consent was obtained from each patient.

2.2. Classification of PAD. A PAD was defined endoscopically as a depressed lesion of 5 mm or more with intact mucosa within a radius of 2.5 cm of the papilla [4]. PAD were classified as type 1, 2, or 3 according to the position of the major papilla from the endoscopic view [5]: type 1, the major papilla was located inside of the diverticula; type 2, the major papilla was located at the edge of the diverticula; type 3, the major papilla was located outside of the diverticula. The sizes of PAD were measured by using a Triple-Lumen Sphincterotome with a scale on the tip (Ultratome™ XL Triple-Lumen Sphincterotome, model number M00535900, BOSTON SCIENTIFIC) during ERCP. The largest diameter of the PAD among length, breadth, and height was chosen as its representative.

2.3. Methods. The examinations were performed using a standard technique and duodenoscopes by a hepatobiliary surgeon. Successful cannulation was defined as free and deep instrumentation of the biliary tree and a cannulation attempt was defined as sustained contact with the cannulating device and the papilla for at least five seconds [6]. Post-ERCP complications include post-ERCP pancreatitis and gastrointestinal perforation.

2.4. Assessment of Recurrent CBD Stones. Patients with CBD stones who underwent the therapeutic ERCP among the 850 patients were followed up until the date of last follow-up as of January 2015. The recurrence of CBD stones was defined as the development of stones according to appropriate imaging studies not earlier than 6 months after the confirmation of complete removal of the CBD stones by ERCP. The exclusion criteria specified a recurrence of CBD stones within 6 months after ERCP. Recurrence-free survival was measured from the complete stones removal to occurrence of new onset, imaging-proven biliary stones requiring hospitalization for ERCP. Data on patients who were recurrence-free were censored on the date of last follow-up.

2.5. Statistical Analysis. For statistical analysis of the categorical data, the chi-square test or Fisher exact test was used. To evaluate the effect of the continuous variable, Student's *t*-test was used. Odds ratios and their 95% confidence intervals were calculated. For adjustment for possible confounders and effect modifiers, multivariate analyses were performed using logistic regression model. The actuarial probability curves for patients remaining free of recurrence of symptomatic CBD stones were constructed using the Kaplan-Meier analysis and compared with the log-rank test. All data analyses were performed using the SPSS statistical software program, version 19.0 (SPSS Inc., Chicago, IL, USA) for Windows and GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA). $P < 0.05$ was considered as statistically significant.

3. Results

3.1. Clinical Characteristics according to the Presence of PAD. There were 161 patients (18.9%) with 1 or more diverticula for whom sufficient data were available for this study. A single diverticula was evident in 80.7% of patients with PAD, 18.6% had 2 diverticula, and 0.7% had more than 2 diverticula. As shown in Table 1, the age and male-to-female ratio between the two study groups were balanced.

The incidences of biliary tract disorders in patients with PAD and controls are shown in Table 1. PAD was correlated with CBD stones (59.6% versus 35.0% in controls; $P < 0.001$) as well as with a higher previous cholecystectomy rate (39.1% versus 24.0% in controls; $P < 0.001$). However, there was no significant difference in the incidence of gall stones only (7.5% versus 9.5% in controls; $P = 0.428$) and gall stones with CBD stones (6.2% versus 11.4% in controls; $P = 0.068$) between the PAD group and the control group. Interestingly, compared to the control group, the detection rate of benign bile duct strictures (8.1% versus 14.7% in controls; $P = 0.031$) and periampullary carcinoma (6.8% versus 21.5% in controls; $P < 0.001$) was significantly lower in the PAD group.

In patients with PAD, acute pancreatitis, defined as pain and serum amylase elevation more than 3 times the normal value, was not found significantly more often than in control patients (31.7% versus 25.9%; $P = 0.154$). Chronic pancreatitis was found with equal frequency in both groups, 3.1% in PAD versus 1.9% ($P = 0.355$) in controls (Table 1).

Regarding the technical success of ERCP, there were no significant differences between the PAD group and controls in terms of successful duct cannulation (95.0% versus 91.9% in controls; $P = 0.190$). Severe post-ERCP pancreatitis, defined as abdominal pain and serum amylase elevation of 3 times the normal value, was observed in 16.1% of PAD group patients and 12.6% of controls ($P = 0.258$). Retroperitoneal perforation was rarely seen and no difference was detected in the perforation rate between two groups (1.2% versus 2.5% in controls; $P = 0.535$) (Table 1).

The abovementioned univariate P values have to be regarded as descriptive. For adjustment for possible confounders and effect modifiers, a multivariate logistic regression model was used with the independent variables which are confirmed to be statistically significant by univariate analysis (Table 1). If those confirmatory multivariate P values are considered, CBD stones only ($P = 0.008$) and periampullary malignancy ($P = 0.004$) remain significant (Table 1).

3.2. Clinical Characteristics according to the PAD Subtypes. The relative frequency of PAD was further stratified according to the subtype: 9.9% of PAD was diagnosed as type 1, 28.0% as type 2, and 62.1% as type 3. The existence of PAD subtypes was correlated with differences in clinical characteristics (Table 2).

The PAD size (mean ± SD) in patients with type 1 PAD was 18.9 ± 9.2 mm, which was significantly larger than that in patients with type 2 PAD (12.1 ± 4.7 mm, $P = 0.003$) or type 3 PAD (10.6 ± 8.6 mm, $P < 0.001$). Similarly, the occurrence of acute pancreatitis was more frequent (62.5%) in patients with type 1 PAD, and it was approximately 2 times higher than

Table 1: Comparison of cholangiopancreatic disorders and technical success of ERCP according to the presence of PAD.

	PAD (n = 161)	Control (n = 483)	P_u*	P_m†	Odds ratio [95% CI]
Median age (yr) (range)	62 (23–90)	61 (26–87)	0.542		
Gender: n (%)					
Male	83 (51.6)	249 (51.6)	1.000		
Female	78 (48.4)	234 (48.4)			
Biliary disorders: n (%)					
CBD and gall stones	10 (6.2)	55 (11.4)	0.068		
CBD stones only	96 (59.6)	169 (35.0)	<0.001	0.008	2.09 [1.213–3.602]
Gall stones only	12 (7.5)	46 (9.5)	0.428		
Benign bile duct strictures	13 (8.1)	71 (14.7)	0.031	0.154	0.61 [0.311–1.203]
Periampullary carcinoma	11 (6.8)	104 (21.5)	<0.001	0.004	0.35 [0.174–0.710]
Previous cholecystectomy	63 (39.1)	116 (24.0)	<0.001	0.712	1.10 [0.653–1.867]
Pancreatic disorders: n (%)					
Acute pancreatitis	51 (31.7)	125 (25.9)	0.153		
Chronic pancreatitis	5 (3.1)	9 (1.9)	0.349		
Successful cannulation: n (%)	153 (95.0)	444 (91.9)	0.190		
Complications: n (%)					
Post-ERCP pancreatitis	26 (16.1)	61 (12.6)	0.258		
Perforation	2 (1.2)	12 (2.5)	0.533		

*Student's t-test for continuous variables and Pearson's chi-square test for categorical variables.
†The multivariate logistic regression model included variables which are confirmed to be statistically significant by univariate analysis as independent variables and PAD as dependent variable.
CBD: common bile duct; ERCP: endoscopic retrograde cholangiopancreatography.

Table 2: Cholangiopancreatic disorders and technical success of ERCP in different PAD subtypes.

	Type 1 (n = 16)	Type 2 (n = 45)	Type 3 (n = 100)	P value*
Median age (yr) (range)	65 (51–78)	66 (24–90)	58 (23–88)	0.134
Gender: n (%)				
Male	9 (56.3)	28 (62.2)	46 (46.0)	0.180
Female	7 (43.8)	17 (37.8)	54 (54.0)	
PAD size (mean ± SD, mm)	18.9 ± 9.2	12.1 ± 4.7	10.6 ± 8.6	0.001
Biliary disorders: n (%)				
CBD stones and gall stones	2 (12.5)	3 (6.7)	5 (5.0)	0.508
CBD stones only	13 (81.3)	26 (57.8)	57 (57.0)	0.177
Gall stones only	1 (6.3)	3 (6.7)	8 (8.0)	0.943
Benign bile duct strictures	0 (0.0)	4 (8.9)	9 (9.0)	0.458
Periampullary carcinoma	0 (0.0)	2 (4.4)	9 (9.0)	0.314
Previous cholecystectomy	9 (56.3)	15 (33.3)	39 (39.0)	0.272
Pancreatic disorders: n (%)				
Acute pancreatitis	10 (62.5)	13 (28.9)	28 (28.0)	0.020
Chronic pancreatitis	1 (6.3)	2 (4.4)	2 (2.0)	0.549
Successful cannulation: n (%)	15 (93.8)	44 (97.8)	94 (94.0)	0.607
Complications: n (%)				
Post-ERCP pancreatitis	2 (12.5)	8 (17.8)	16 (16.0)	0.884
Perforation	0 (0.0)	1 (2.2)	1 (1.0)	0.740

*One-way analysis of variance for continuous variables and Pearson's chi-square test or Fisher exact test for categorical variables.
CBD: common bile duct; ERCP: endoscopic retrograde cholangiopancreatography.

Table 3: Univariate analysis of the risk factors for recurrence of symptomatic CBD stones.

	Recurrence group (n = 32)	Nonrecurrence group (n = 269)	P value*
Median age (yr) (range)	62.5 (44–78)	61 (27–90)	0.360
Gender: n (%)			
Male	18 (56.3)	131 (48.7)	0.419
Female	14 (43.8)	138 (51.3)	
CBD diameter (mean ± SD, mm)	14.5 ± 4.6	14.3 ± 8.3	0.957
CBD stone size (mean ± SD, mm)	11.5 ± 6.4	11.5 ± 7.1	0.984
CBD stone number: n (%)			
1	8 (25.0)	93 (34.6)	0.278
≥2	24 (75.0)	176 (65.4)	
PAD: n (%)	18 (56.3)	79 (29.4)	0.002
Type 1	6 (18.8)	7 (2.6)	
Type 2 + type 3	12 (37.5)	72 (26.8)	
Prior cholecystectomy: n (%)	25 (78.1)	141 (52.4)	0.006
ERCP attempt: n (%)			
1	26 (81.2)	239 (88.8)	0.211
≥2	6 (18.8)	30 (11.2)	
Lithotripsy: n (%)	6 (18.8)	37 (13.8)	0.445
EST: n (%)	22 (68.8)	214 (79.6)	0.160
EPBD: n (%)	24 (75.0)	221 (82.2)	0.325
Successful cannulation: n (%)	31 (88.1)	256 (93.4)	0.665

*Student's t-test for continuous variables and Pearson's chi-square test for categorical variables.
CBD: common bile duct; EST: endoscopic sphincterotomy; EPBD: endoscopic papillary balloon dilation.

patients with type 2 PAD (28.9%, $P = 0.017$) or type 3 PAD (28.0%, $P = 0.006$). In addition, CBD stones alone showed higher tendency in type 1 PAD than in type 2 or type 3 PAD although it did not reach a statistical significance. Moreover, there were no significantly different characteristics between patients with type 2 and type 3 PAD.

3.3. Risk Factors for the Recurrence of Symptomatic CBD Stones. 330 patients were diagnosed to have symptomatic CBD stones in this study. In order to study the risk factors of recurrence of symptomatic CBD stones after therapeutic ERCP, a total of 301 patients were finally enrolled (29 patients were excluded due to the follow-up loss or recurrence of CBD stones within 6 months after ERCP). The median follow-up was 40 months (6–76 months). The recurrence of CBD stones occurred in 32 patients (10.6%) during the follow-up period, and the median time until the first recurrence was 36 months (6–60 months).

After the univariate analysis and the multivariate logistic regression analysis of the potential risk factors of the recurrence of symptomatic CBD stones after therapeutic ERCP, we found that PAD (odds ratio [OR] = 2.968, [95% CI, 1.394–6.321], $P = 0.005$) and prior cholecystectomy (odds ratio [OR] = 3.106, [95% CI, 1.287–7.496], $P = 0.012$) were the two independent risk factors (Table 3).

The actuarial probability of patients remaining free of recurrence of symptomatic CBD stones during the follow-up after therapeutic ERCP with PAD was significantly lower than that for the patients without PAD (81.4% versus 93.1%, resp.; $P = 0.004$, log-rank test) (Figure 1(a)). Subgroup analysis showed that the patients with type 1 PAD had significantly lower rates of being free of recurrence of CBD stones during the follow-up than did the patients who had type 2 or type 3 PAD (53.8% versus 85.7%, resp.; $P = 0.043$, log-rank test) (Figure 1(b)). Since PAD and prior cholecystectomy were two independent risk factors for recurrence of symptomatic CBD stones after therapeutic ERCP, another subgroup analysis was performed to determine if there was a differential recurrence-free probability between patients with or without PAD who underwent previous cholecystectomy. The PAD patients who underwent previous cholecystectomy had a significantly lower rate of being free of recurrence of CBD stones than the patients without PAD (42/58, 72.4% versus 99/108, 91.7%, resp.; $P = 0.001$, log-rank test) (Figure 1(c)), whereas in patients with gall bladder in situ, PAD did not have a promoting effect on recurrence of CBD stones as the recurrence-free rate was similar between the patients with or without PAD (37/39, 94.9% versus 91/96, 94.8%, resp.; $P = 0.886$, log-rank test) (Figure 1(d)). However, due to the small number of recurrences in patients with gall bladder in situ, the statistical power was limited.

4. Discussion

In this study, we sought to demonstrate the association of different types of PAD with occurrent and recurrent bile duct stones, with pancreatitis, and with the technical success of ERCP.

PAD, not uncommon findings during ERCP, has been reported to be associated with biliary diseases [2]. Since the incidence of both PAD and bile duct stones increases with

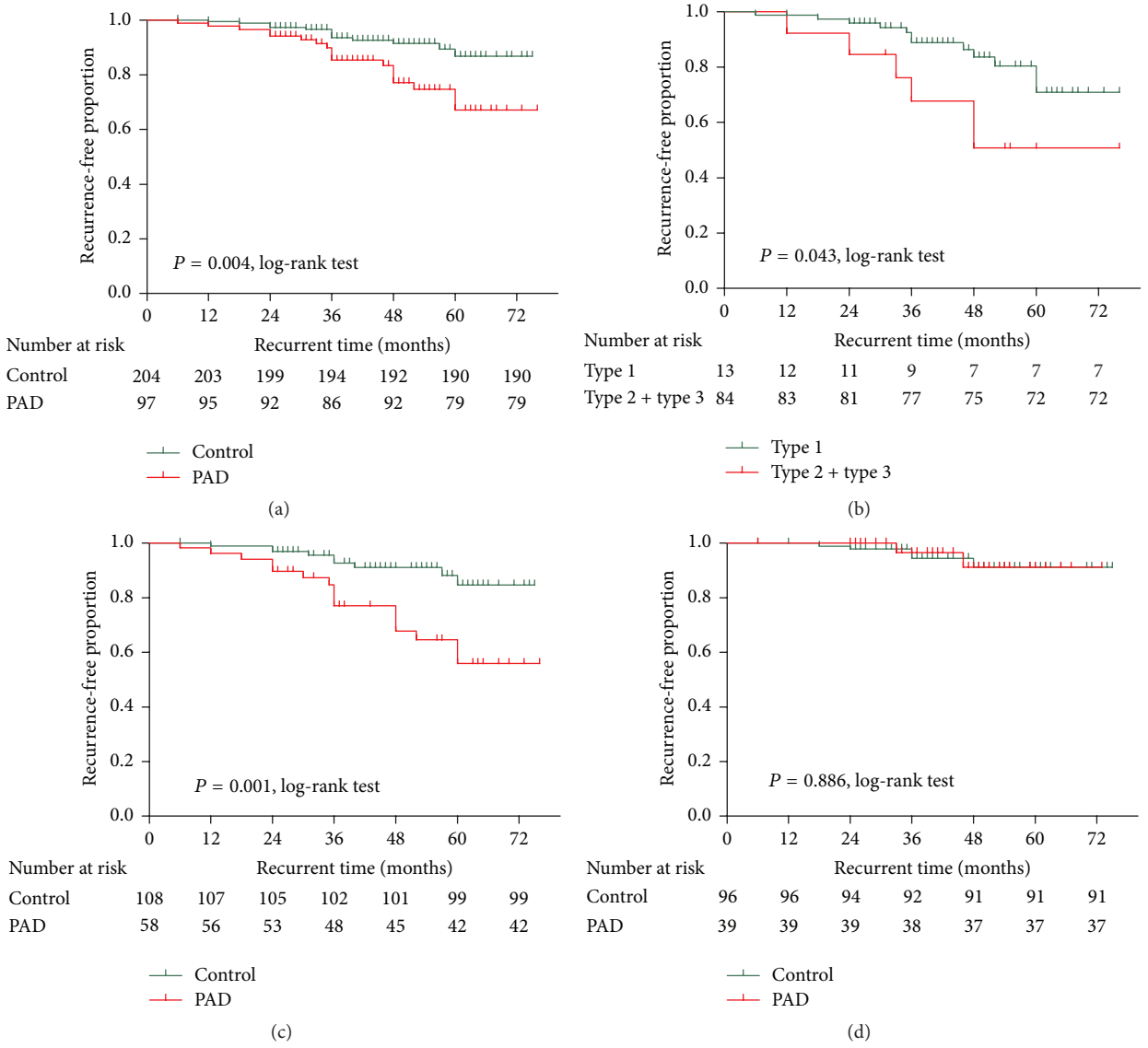

Figure 1: The actuarial probability of patients remaining free of recurrence of symptomatic CBD stones during the follow-up after therapeutic ERCP. (a) The patients with PAD versus those without PAD; (b) the patients with type 1 PAD versus those with type 2 or type 3 PAD; (c) recurrence-free probability between the two groups who underwent previous cholecystectomy; (d) recurrence-free probability between the two groups with gall bladder in situ.

age [7, 8], our study adjusted this confounding variable and found that the prevalence of PAD was increased in patients with CBD stones but not in those with gallbladder stones alone, which confirms the findings from other reports that PAD is associated with bile duct stones [9–11]. Furthermore, type 1 PAD, in which the major papilla is located within the diverticula, is considered to carry a theoretically greater risk of biliary stones formation [5]. Consistent with this speculation, we noted that common bile duct stones were relatively more common in type 1 PAD patients (81.7%) when compared to patients with type 2 and type 3 PAD (57.8%, 57.0%, resp.) although it did not reach to a statistical difference. As such, these results strongly suggest a causal relationship between PAD and biliary stones formation. The pathological mechanism of this association is explained by several hypotheses. The mechanical pressure of the diverticula to the distal end of the biliary tract is commonly discussed. The larger the PAD and the closer it is to a papilla, the more it may disturb the bile flow [12]. Another hypothesis is related to the dysfunction of the sphincter of Oddi (SO), which is believed to be caused by the accumulation of food in the diverticula, compressing the end of the bile duct as well as SO and leading to stricture of the sphincter. The dysfunction of the SO leads to the reflux of gastrointestinal juice into the bile duct, bacterial infection of the bile duct, and formation of the pigment bile duct stones [1, 3, 13, 14].

In addition, we noted that the presence of PAD is negatively associated with prevalence of periampullary carcinoma which to our knowledge has not been reported before. However, there were some studies trying to investigate

the relationship between diverticulosis, diverticulitis, polyps, advanced neoplastic lesions (ANL), and colorectal carcinoma (CRC). One study from Korea found an increased risk of CRC in both patients with left- or right-sided diverticulosis without prior polypectomy or surgery in the affected area [15]. One of the possible explanations for the association between diverticular disease and colorectal cancer is that the presence of inflammation process increases the risk of malignant transformation. In contrast, three studies [16–18] showed no relationship between diverticulosis and CRC, one of them being a longitudinal study [16]. Moreover, another three studies [19–21] found less CRC in patients with diverticular disease, which speak in favor of what we observed that periampullary malignancy is less common in PAD patients. One possible explanation is that an altered matrix composition predisposes to the development of colon cancer in the colonic tissue architecture of cancer patients but not in patients with diverticular disease [22]. According to these literature reviews, we considered one hypothesis to explain the negative correlation between periampullary malignancy and PAD. That is, there may be a more protumorigenic matrix microenvironment in the periampullary tissue architecture in the patients without PAD compared to those with PAD, which is in accordance with no predisposition for cancer in diverticular disease in these patients. Starting from this point, our future work is to investigate the detailed microenvironment composition of periampullary tissue in patients with periampullary malignancy or patients with different types of PAD by using tissue and gene microarray analyses. These approaches would be a powerful tool in grouping cancer patients into classes with clinical and therapeutic relevance. Clearly, the longitudinal study following cohorts of patients with diverticulosis or diverticulitis instead of cross-sectional study is the best way to analyze the causality between diverticulosis and periampullary malignancy. Therefore, we will also start a longitudinal study in the near future following cohorts of patients with PAD and try to clarify this causality.

It has been a matter of dispute whether or not pancreatitis is induced by PAD per se. Some investigators have suggested that pancreatitis is not associated with PAD [9, 23]. Others reported that patients with PAD have a higher rate of acute pancreatitis [24, 25]. Our study did not find a significant higher rate of pancreatitis in PAD patients than in patients without PAD. However, we found that the type 1 PAD patients had a bigger PAD size and a higher frequency of acute pancreatitis than the patients with type 2 or type 3 PAD. From this observation we might hypothesize that the distension of diverticula with specific location (papilla located inside of the diverticula) may cause compression of the pancreatic duct and result in pancreatitis. As described above, PAD predispose the patient to common bile duct stones; it is difficult to tell whether pancreatitis is from biliary origin or by the diverticula themselves. But at least, the presence of PAD should be taken into account, mainly in elderly patients, before defining a pancreatitis as idiopathic.

PAD is thought to be an impediment to ERCP procedures. Although successful cannulation in patients with PAD varies from 61% to 95.4%, this was found to be significantly lower compared with patients without PAD in some studies [24, 26, 27]; however, some other papers showed that the successful cannulation rate and morbidity and mortality rates after ERCP were almost the same between patients with and without PAD [4, 9, 28, 29]. The various techniques for cannulation, the experience of the operators, the different patient characteristics, and the lack of adjustment for those variables between the exposed and control groups can all be responsible for explaining the lack of consistency in results so far. Our study has the advantage of including a concrete sample of Chinese patients treated by the same experienced surgeon in a university hospital. We found no difference in successful cannulation between patients with and without PAD, irrespective of the location of the papilla.

In clinical practice, a considerate number of patients visit the hospital for management of the recurrence of symptomatic CBD stones. In this situation, identifying the risk factors for the development of recurrent CBD stones is needed. In this study, the independent risk factors for the recurrence of symptomatic CBD stones were PAD and prior cholecystectomy. PAD has been advocated as a factor for recurrence of CBD stones in several previous studies [30–32], yet this is still controversial. Ando et al. [14] did not regard the periampullary diverticula as a risk factor for recurrent bile duct stones after endoscopic papillotomy. Kim et al. [33] addressed that periampullary diverticula is associated with patients with primary common bile duct stones, but not with the secondary ones. However, in our study, the presence of PAD was the independent risk factor of the recurrence of symptomatic CBD stones after therapeutic ERCP. More specifically, type 1 PAD, with the papilla located within the diverticula, was correlated with a shorter recurrence time of symptomatic CBD stones. This is consistent with the study of Kim et al. [5] and the study of Baek et al. [34] which both suggested that type 1 PAD was related to recurrence of CBD stones. The factor of prior cholecystectomy was considered as another independent risk factor for recurrence of CBD stones in our study. In subgroup analysis we found that, in the patients with an intact gall bladder, PAD did not increase the CBD stones recurrence rate. It is probable that gall bladder motility is related to the low recurrence rate of CBD stones. Several authors proved that significant improvement in gall bladder motility was achieved after therapeutic ERCP [35, 36]. It is also noted that bile stasis is an important factor in the pathogenesis of bile duct stone formation. Frossard et al. [37] evaluated 92 patients with CBD stones and reported that the presence of the gall bladder was significantly associated with spontaneous bile duct stone passage. These positive roles of gall bladder may neutralize the ill effects of PAD in the recurrence of symptomatic CBD stones. However, in patients with prior cholecystectomy, the relative risk of the PAD group was significantly higher than that of the group without PAD (risk ratio [RR] = 4.034, [95% CI, 1.742–9.346], $P = 0.001$). It is probable that cholecystectomy can result in some secondary changes like the dysfunction of the sphincter of Oddi, common bile duct dilatation, long cystic duct stump, and bile duct angulation which were very important factors in the pathogenesis of bile duct stone formation [38–40]. In addition, the slow biliary emptying and bile stasis in patients with PAD [30] may have a synergetic effect with the

secondary changes induced by cholecystectomy in forming the recurrence of CBD stones. Therefore, careful periodic surveillance of blood tests, ultrasonography, and/or magnetic resonance cholangiography may be recommended for CBD patients who present with PAD with prior cholecystectomy after therapeutic ERCP.

In conclusion, this study demonstrates that PAD, especially type 1 PAD, is associated with an increased occurrence and recurrence of CBD stones. Acute pancreatitis is more frequent in patients with type 1 PAD than patients with type 2 or type 3 PAD. PAD during an ERCP should not be considered an obstacle to a successful cannulation.

Competing Interests

The authors declare that they have no competing interests.

References

[1] D. N. Lobo, T. W. Balfour, S. Y. Iftikhar, and B. J. Rowlands, "Periampullary diverticula and pancreaticobiliary disease," *British Journal of Surgery*, vol. 86, no. 5, pp. 588–597, 1999.

[2] N. Egawa, H. Anjiki, K. Takuma, and T. Kamisawa, "Juxtapapillary duodenal diverticula and pancreatobiliary disease," *Digestive Surgery*, vol. 27, no. 2, pp. 105–109, 2010.

[3] B. Ozogul, G. Ozturk, A. Kisaoglu, B. Aydinli, M. Yildirgan, and S. S. Atamanalp, "The clinical importance of different localizations of the papilla associated with juxtapapillary duodenal diverticula," *Canadian Journal of Surgery*, vol. 57, no. 5, pp. 337–341, 2014.

[4] P. Tyagi, P. Sharma, B. C. Sharma, and A. S. Puri, "Periampullary diverticula and technical success of endoscopic retrograde cholangiopancreatography," *Surgical Endoscopy and Other Interventional Techniques*, vol. 23, no. 6, pp. 1342–1345, 2009.

[5] C. W. Kim, J. H. Chang, J. H. Kim, T. H. Kim, I. S. Lee, and S. W. Han, "Size and type of periampullary duodenal diverticula are associated with bile duct diameter and recurrence of bile duct stones," *Journal of Gastroenterology and Hepatology*, vol. 28, no. 5, pp. 893–898, 2013.

[6] A. H. Mohammad Alizadeh, E. S. Afzali, A. Shahnazi et al., "ERCP features and outcome in patients with periampullary duodenal diverticulum," *ISRN Gastroenterology*, vol. 2013, Article ID 217261, 5 pages, 2013.

[7] G. Novacek, M. Walgram, P. Bauer, R. Schöfl, A. Gangl, and R. Pötzi, "The relationship between juxtapapillary duodenal diverticula and biliary stone disease," *European Journal of Gastroenterology and Hepatology*, vol. 9, no. 4, pp. 375–379, 1997.

[8] R. H. Kennedy and M. H. Thompson, "Are duodenal diverticula associated with choledocholithiasis?" *Gut*, vol. 29, no. 7, pp. 1003–1006, 1988.

[9] T. C. K. Tham and M. Kelly, "Association of periampullary duodenal diverticula with bile duct stones and with technical success of endoscopic retrograde cholangiopancreatography," *Endoscopy*, vol. 36, no. 12, pp. 1050–1053, 2004.

[10] E. Christoforidis, I. Goulimaris, I. Kanellos, K. Tsalis, and I. Dadoukis, "The role of juxtapapillary duodenal diverticula in biliary stone disease," *Gastrointestinal Endoscopy*, vol. 55, no. 4, pp. 543–547, 2002.

[11] X. Li, K. Zhu, L. Zhang et al., "Periampullary diverticulum may be an important factor for the occurrence and recurrence of bile duct stones," *World Journal of Surgery*, vol. 36, no. 11, pp. 2666–2669, 2012.

[12] Y. Kubota, T. Yamaguchi, K. Tani et al., "Anatomical variation of pancreatobiliary ducts in biliary stone diseases," *Abdominal Imaging*, vol. 18, no. 2, pp. 145–149, 1993.

[13] C. Van Nieuwkoop, I. Boere, P. A. M. Rosekrans, and D. J. Bac, "Recurrent bacterial cholangitis due to a juxtapapillary diverticulum," *European Journal of Gastroenterology and Hepatology*, vol. 14, no. 2, pp. 189–190, 2002.

[14] T. Ando, T. Tsuyuguchi, T. Okugawa et al., "Risk factors for recurrent bile duct stones after endoscopic papillotomy," *Gut*, vol. 52, no. 1, pp. 116–121, 2003.

[15] C. S. Choi, S. C. Choi, G. S. Seo et al., "Association between diverticulosis and colonic neoplasm in Koreans," *The Korean Journal of Gastroenterology*, vol. 49, no. 6, pp. 364–368, 2007.

[16] T. Stefánsson, A. Ekbom, P. Sparèn, and L. Påhlman, "Association between sigmoid diverticulitis and left-sided colon cancer: a nested, population-based, case control study," *Scandinavian Journal of Gastroenterology*, vol. 39, no. 8, pp. 743–747, 2004.

[17] A. Soran, A. Harlak, J. W. Wilson et al., "Diverticular disease in patients with colon cancer: subgroup analysis of national surgical adjuvant breast and bowel project protocol C-06," *Clinical Colorectal Cancer*, vol. 6, no. 2, pp. 140–145, 2006.

[18] S. Morini, C. Hassan, A. Zullo et al., "Diverticular disease as a risk factor for sigmoid colon adenomas," *Digestive and Liver Disease*, vol. 34, no. 9, pp. 635–639, 2002.

[19] R. J. L. F. Loffeld and A. B. M. M. Van Der Putten, "Diverticular disease of the colon and concomitant abnormalities in patients undergoing endoscopic evaluation of the large bowel," *Colorectal Disease*, vol. 4, no. 3, pp. 189–192, 2002.

[20] C. J. Krones, U. Klinge, N. Butz et al., "The rare epidemiologic coincidence of diverticular disease and advanced colonic neoplasia," *International Journal of Colorectal Disease*, vol. 21, no. 1, pp. 18–24, 2006.

[21] M. M. Meurs-Szojda, J. S. T. S. Droste, D. J. Kuik, C. J. J. Mulder, and R. J. F. Felt-Bersma, "Diverticulosis and diverticulitis form no risk for polyps and colorectal neoplasia in 4,241 colonoscopies," *International Journal of Colorectal Disease*, vol. 23, no. 10, pp. 979–984, 2008.

[22] U. Klinge, R. Rosch, K. Junge et al., "Different matrix microenvironments in colon cancer and diverticular disease," *International Journal of Colorectal Disease*, vol. 22, no. 5, pp. 515–520, 2007.

[23] T. Zoepf, D.-S. Zoepf, J. C. Arnold, C. Benz, and J. F. Riemann, "The relationship between juxtapapillary duodenal diverticula and disorders of the biliopancreatic system: analysis of 350 patients," *Gastrointestinal Endoscopy*, vol. 54, no. 1, pp. 56–61, 2001.

[24] M. K. Leivonen, J. A. A. Halttunen, and E. O. Kivilaakso, "Duodenal diverticulum at endoscopic retrograde cholangiopancreatography, analysis of 123 patients," *Hepato-Gastroenterology*, vol. 43, no. 10, pp. 961–966, 1996.

[25] G. Uomo, G. Manes, A. Ragozzino, A. Cavallera, and P. G. Rabitti, "Periampullary extraluminal duodenal diverticula and acute pancreatitis: an underestimated etiological association," *The American Journal of Gastroenterology*, vol. 91, no. 6, pp. 1186–1188, 1996.

[26] A. Rajnakova, P. M. Y. Goh, S. S. Ngoi, and S. G. Lim, "ERCP in patients with periampullary diverticulum," *Hepato-Gastroenterology*, vol. 50, no. 51, pp. 625–628, 2003.

[27] K. S. Ko, S. H. Kim, H. C. Kim, I. H. Kim, and S.-O. Lee, "Juxtapapillary duodenal diverticula risk development and recurrence of biliary stone," *Journal of Korean Medical Science*, vol. 27, no. 7, pp. 772–776, 2012.

[28] J. Boix, V. Lorenzo-Zúñiga, F. Añaños, E. Domènech, R. M. Morillas, and M. A. Gassull, "Impact of periampullary duodenal diverticula at endoscopic retrograde cholangiopancreatography: a proposed classification of periampullary duodenal diverticula," *Surgical Laparoscopy, Endoscopy and Percutaneous Techniques*, vol. 16, no. 4, pp. 208–211, 2006.

[29] V. Panteris, A. Vezakis, G. Filippou, D. Filippou, D. Karamanolis, and S. Rizos, "Influence of juxtapapillary diverticula on the success or difficulty of cannulation and complication rate," *Gastrointestinal Endoscopy*, vol. 68, no. 5, pp. 903–910, 2008.

[30] K. H. Lai, N. J. Peng, G. H. Lo et al., "Prediction of recurrent choledocholithiasis by quantitative cholescintigraphy in patients after endoscopic sphincterotomy," *Gut*, vol. 41, no. 3, pp. 399–403, 1997.

[31] O. Sandstad, T. Osnes, V. Skar, P. Urdal, and M. Osnes, "Common bile duct stones are mainly brown and associated with duodenal diverticula," *Gut*, vol. 35, no. 10, pp. 1464–1467, 1994.

[32] A. Ohashi, K. Tamada, S. Wada et al., "Risk factors for recurrent bile duct stones after endoscopic papillary balloon dilation: long-term follow-up study," *Digestive Endoscopy*, vol. 21, no. 2, pp. 73–77, 2009.

[33] M.-H. Kim, S. J. Myung, D. W. Seo et al., "Association of periampullary diverticula with primary choledocholithiasis but not with secondary choledocholithiasis," *Endoscopy*, vol. 30, no. 7, pp. 601–604, 1998.

[34] Y. H. Baek, H. J. Kim, J. H. Park et al., "Risk factors for recurrent bile duct stones after endoscopic clearance of common bile duct stones," *The Korean Journal of Gastroenterology*, vol. 54, no. 1, pp. 36–41, 2009.

[35] M. Sugiyama and Y. Atomi, "Long term effects of endoscopic sphincterotomy on gall bladder motility," *Gut*, vol. 39, no. 6, pp. 856–859, 1996.

[36] B. C. Sharma, D. K. Agarwal, S. S. Baijal, T. S. Negi, G. Choudhuri, and V. A. Saraswat, "Effect of endoscopic sphincterotomy on gall bladder bile lithogenicity and motility," *Gut*, vol. 42, no. 2, pp. 288–292, 1998.

[37] J. L. Frossard, A. Hadengue, G. Amouyal et al., "Choledocholithiasis: a prospective study of spontaneous common bile duct stone migration," *Gastrointestinal Endoscopy*, vol. 51, no. 2, pp. 175–179, 2000.

[38] M. Yaghoobi, Q. Pauls, V. Durkalski et al., "Incidence and predictors of post-ERCP pancreatitis in patients with suspected sphincter of Oddi dysfunction undergoing biliary or dual sphincterotomy: results from the EPISOD prospective multicenter randomized sham-controlled study," *Endoscopy*, vol. 47, no. 10, pp. 884–890, 2015.

[39] D. B. Seo, B. W. Bang, S. Jeong et al., "Does the bile duct angulation affect recurrence of choledocholithiasis?" *World Journal of Gastroenterology*, vol. 17, no. 36, pp. 4118–4123, 2011.

[40] M. R. Sahoo and A. Kumar, "Stump stone 6 years after cholecystectomy: a possibility," *BMJ Case Reports*, Article ID 007957, 2013.

Hindawi Publishing Corporation
Gastroenterology Research and Practice
Volume 2016, Article ID 3296801, 7 pages
http://dx.doi.org/10.1155/2016/3296801

Review Article

Malignant Biliary Obstruction: Evidence for Best Practice

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Received 23 October 2015; Accepted 17 January 2016

Academic Editor: Mohamad H. Imam

What should be done next? Is the stricture benign? Is it resectable? Should I place a stent? Which one? These are some of the questions one ponders when dealing with biliary strictures. In resectable cases, ongoing questions remain as to whether the biliary tree should be drained prior to surgery. In palliative cases, the relief of obstruction remains the main goal. Options for palliative therapy include surgical bypass, percutaneous drainage, and stenting or endoscopic stenting (transpapillary or via an endoscopic ultrasound approach). This review gathers scientific foundations behind these interventions. For operable cases, preoperative biliary drainage should not be performed unless there is evidence of cholangitis, there is delay in surgical intervention, or intense jaundice is present. For inoperable cases, transpapillary stenting after sphincterotomy is preferable over percutaneous drainage. The use of plastic stents (PS) has no benefit over Self-Expandable Metallic Stents (SEMS). In case transpapillary drainage is not possible, Endoscopic Ultrasonography- (EUS-) guided drainage is still an option over percutaneous means. There is no significant difference between the types of SEMS and its indication should be individualized.

1. Introduction

Neoplasms that affect the bile duct are uncommon [1–5]. Despite their rarity, estimates from the Surveillance, Epidemiology and End Results (SEER) database from North America reveal an increased incidence and a poor prognosis. The calculated prevalence in 2012 was 15 per 100,000 people [6]. It is estimated that almost 20% of the subclinical jaundice is due to malignant bile duct obstruction [7], divided by a ratio of 2 : 1 of pancreatic and other biliary obstructive cancers, respectively [8]. The most common causes of malignant biliary obstruction (MBO) are pancreatic adenocarcinoma, cholangiocarcinoma, ampullary/duodenal adenocarcinoma, gallbladder adenocarcinoma, lymphoma, and compressive metastatic proximal lymph nodes [9, 10].

Despite technological advances, only 20% of periampullary tumors are found to be resectable at the time of presentation due to their invasiveness, late symptom appearance, and onset in elderly people [11–13]. According to the Brazilian National Institute of Cancer (INCA), pancreatic tumors were accountable for 2% of the malignant tumors with an estimate of around 17,000 new cases in 2015. Having in mind that only 15%–20% of these neoplasms are resectable, the number of inoperable MBO in Brazil in the year of 2015 is estimated to be about 13,000 patients [14].

Biliary tree obstruction and consequent jaundice occur in 70–90% of these patients and have important consequences mainly for the patient's quality of life, morbidity, and overall mortality [15–19]. Options for palliative therapy of biliary tree obstruction include surgical bypass, percutaneous external drainage/stenting, and endoscopic stenting. For patients with resectable tumors, ongoing debate remains on whether preoperative drainage is necessary. Commonly, MBO appears as painless jaundice with anorexia and weight loss. This can sometimes be present in other benign conditions (i.e., chronic pancreatitis) [9, 10]. Although the diagnosis can be achieved without tissue biopsy, it is important to have histological confirmation. Tissue can be acquired through interventional

radiology (ultrasound/computed tomography-guided puncture) or through endoscopic procedures, such as Endoscopic Retrograde Cholangiopancreatography (ERCP) and Endoscopic Ultrasound-Guided Fine-Needle Aspiration (EUS-FNA), although the former can be associated with seeding in the needle tract [20–23].

To further evaluate a biliary stricture, it may be necessary to perform a computed tomography (CT) scan or a Magnetic Resonance Cholangiopancreatography (MRCP). If a mass is observed, a tissue sample should be obtained via the methods previously mentioned. If no mass is seen, an EUS should be performed and any visualized lesion can be sampled. ERCP with brush cytology, cholangioscopy, endomicroscopy, and/or intraductal ultrasound can be performed to further evaluate this [9, 10, 24].

The European Society of Gastrointestinal Endoscopy's (ESGE) guidelines [25] recommend placing a plastic stent for biliary drainage if a diagnosis of the biliary obstruction (malignant versus benign) is still not ascertained. Despite this recommendation, patients with a high clinical-imaginologic suspicion of MBO (i.e., an elderly male patient, smoker, with high bilirubin levels, anorexia, and metastatic disease on imaging) could benefit in using a fully covered Self-Expandable Metallic Stent (cSEMS), therefore avoiding the cost and possible complications of another ERCP. The current practice however is to place a plastic stent (PS) in cases of cholangitis as there is little data about the possible advantages of SEMS in these cases.

This review intends to explore the possibilities of drainage of the biliary tree in patients with malignant biliary obstruction.

2. Operable Cases

2.1. Preoperative Drainage. The routine use of preoperative biliary drainage (PBD) is not well defined yet, although its use in cholangitis, neoadjuvant therapies, and delayed surgery is advocated by the ESGE.

A meta-analysis from Cochrane [26], involving six randomized controlled trials (RCTs) with percutaneous and endoscopic interventions, revealed major morbidity and no change in mortality in the group who was subjected to preoperative drainage. However the clinical status of patients were rather heterogeneous amongst the studies and the stent used was PS. There is scarce material regarding the use of Self-Expandable Metallic Stents (SEMS) for PBD.

A retrospective study published in January 2015 [27] evaluated the use of percutaneous transhepatic biliary drainage (PTBD) versus SEMS versus PS versus no drainage in PBD. The results demonstrated a significantly higher rate of sterile bile in the no drainage group, although this finding was not translated in less infection in the postprocedure period. There were no differences between SEMS and PS. Nonetheless, the sample had a small percentage of SEMS placed (15%) and the median present bilirubin level was 201 μmol/L. The severity of jaundice is used in clinical practice to infer the severity of the obstruction and is beginning to figure as an important factor to look at in recent articles. Sauvanet et al. [17] published in August 2015 an article demonstrating that a cutoff value of 250–300 μmol/L in serum bilirubin level had clinical impact in patients with recurrent jaundice after pancreaticoduodenectomy due to pancreatic adenocarcinoma, and patients above this cutoff value had higher morbidity and mortality.

A RCT published in August 2015 added information not only regarding drainage or not but also analyzing the types of drainage. It revealed an overall complication rate for cSEMS, PS, and early surgery groups of 51%, 74%, and 39%, respectively [28]. The evidence gathered so far in the use of preoperative drainage indicates that it can be specifically beneficial also in proximal obstructions and there may be a better outcome if SEMS are used [29, 30] in this tendency. More studies are needed to determine a possible benefit in patients with high bilirubin levels and long wait for surgery (either for logistic reasons or for need of clinical compensation/neoadjuvant chemoradiation), as well as the neoplasia's topography most benefited by the drainage and the optimal material for the stent. In any case, if preoperative drainage has been deemed necessary, it is needed to ponder the type of intervention: percutaneous (PTBD) or endoscopic. PTBD has higher morbidity due to the risk of puncture-related hemorrhage, cutaneous infection, and catheter tract recurrence. Percutaneous tract seeding is a major preoccupation and can compromise up to 5.2% of potentially curable cases [31]. Nonetheless, some studies have shown that, in patients with proximal tumors, the endoscopic drainage can have lower technical success (38% of cases) [32] and should preferably have an internal drainage [33]. If PTBD is chosen, sphincterotomy should be performed in transpapillary stent placement; in order to prevent pancreatitis for tumors more than 2 cm in distance from the papillae, a suprapapillary stent could be used as an option for transpapillary stenting [34, 35].

These articles show evidences supporting either therapy. Since they involved data as far as 14 years ago, their data may be not applicable for the current practices and technical success; therefore more studies regarding the type of preoperative drainage are needed for a definitive answer.

In summary, the evidence thus far reveals that, for patients with a low bilirubin level and scheduled early surgery, preoperative drainage should be avoided. On other routine PBD cases, the conflicting data suggests that individual case scenarios should be analyzed.

3. Inoperable Cases

3.1. Palliative Surgical Bypass versus Endoscopic Drainage. Although initial results with surgical bypass demonstrated low rates of recurrent jaundice (2–5%), the surgery itself carries an appreciable risk of postoperative morbidity and mortality, in up to one-fourth of the patients in some trials [36, 37]. Despite the evidence of more complications with surgical decompression, it has been advocated in patients who at the time of laparotomy for planned tumor resection are found to have unresectable disease as well as in occasional patients with longer projected survival due to its longer jaundice relief [38, 39].

In order to analyze the possible treatments for inoperable MBO, RCTs have compared some of these interventions and found that, despite a shorter time for recurrence of jaundice,

the complication rate was lower in the endoscopic group [40, 41]. A recent meta-analysis from 2015 regarding surgical bypass versus endoscopic stenting for distal inoperable MBO demonstrated no differences for success of the procedures, but differences were observed with better outcomes for endoscopic therapy with 10% less mortality and 19% less complications associated with the procedure [42].

In summary, from a palliative perspective, the use of an endoscopic approach appears to be favorable.

3.2. SEMS versus PS. Two main types of materials for stents are routinely used in current practice: plastic and metal. Several RCTs demonstrated that SEMS are associated with longer stent patency but survival rate is quite similar to PS. Some studies favored survival in the SEMS group [43–52] while some favored the PS group [53, 54]. Statistically significant survival difference has only been shown in one study, favoring SEMS [55].

The latest meta-analysis regarding metal and plastic stenting in inoperable MBO [56], which involved stents inserted through ERCP, involved thirteen RCTs and demonstrated a better survival of about 1-2 months in the SEMS group. In this meta-analysis, the use of SEMS had 24% fewer dysfunction, almost double patency (124 days versus 250 days), and longer survival. It also required 30% fewer reinterventions, when compared to PS. Despite no statistical differences in costs and complication amongst the two stents groups, there was numerical difference benefitting SEMS (€4,193.98 for SEMS versus €4,728.65 for PS, $P = 0.09$ and 3% less complication, $P = 0.16$).

Kim et al. [57] demonstrated a survival benefit in metastatic biliary tract cancer of about 9 months in a phase II study of gemcitabine and S-1 combination chemotherapy, in contrast to the 3-4 months survival of earlier studies. This is also true for pancreatic adenocarcinoma that has a mean overall survival of 6.9 months with new treatments [58]. Therefore, taking into account the patients' quality of life and adequate palliative care with the lowest hospital stay possible and minimal symptomatology, SEMS is always the first option.

An important aspect is to look at the whole treatment cost rather than the cost of the specific instrument. Therefore, a prospective randomized controlled study with attention to a specific population (short expected survival) is needed to clarify if SEMS is actually more cost-effective in this group.

The summary of evidences presented so far points out that the use of SEMS is advisable. Even in the short expected survival cases, the question we should ask ourselves is why not use SEMS, as it does not cost more, has similar complication, and does have better outcomes [56].

3.3. Types of SEMS. Endoscopic stents appear to offer a less invasive option, but the many designs and stent types available have made selecting the ideal stent for individual patients complicated. There are several combinations of materials, with or without antireflux valves, uncovered SEMS (uSEMS), partially covered SEMS (pcSEMS) or cSEMS, and different kinds of mesh. All of them have different possible complications and conflicting information in the literature [59–63]. To date, two meta-analyses demonstrated no benefits to survival or morbidity in cSEMS compared to uSEMS [64, 65]. There is still no SEMS that has presented a far superior result compared to the others.

Usually uSEMS are associated with obstruction due to ingrowth while cSEMS have higher migration rates and association with cholecystitis if placed across the cystic duct in patients not cholecystomized [59, 64]. A retrospective study from 2013 evaluated uSEMS versus cSEMS and found that the adverse event rate is about 27% for both, tumor ingrowth with recurrent obstruction is more common in the uSEMS group (76% versus 9%, $P < 0.001$), and stent migration is more common in cSEMS group (36% versus 2%, $P < 0.001$) [62]. A more recent pcSEMS was developed, trying to gather the best of both worlds. Apparently, it has better results with less stent migration than cSEMS but more than uSEMS (pcSEMS 5.9% versus uSEMS 0%, $P = 0.118$) and less tumor ingrowth than uSEMS (pcSEMS 5.9% versus uSEMS 19.2%, $P = 0.041$) [63].

The major causes of dysfunction of the large bore cSEMS are attributed to the reflux of duodenal content into the prosthesis and to the stent migration. Although studies with innovative mechanisms to surpass the migration problem failed to show any difference [63], the antireflux mechanism has shown to lead to longer patency. In the study by Lee et al. [66], the overall reflux of barium was 7.7% in the Anti-Reflux Valve Metal Stent (ARVMS) group versus 100% in the cSEMS group and the cumulative median duration of stent patency was 407 days for ARVMS versus 220 days for cSEMS.

In order to overcome the main problem of obstruction due to tumor ingrowth when using the uSEMS, the use of novel SEMS that are combined with radioactive seeds (I125) or brachytherapy is still being studied and has shown promising results regarding patency time and survival (mean survival of 8 months versus 3 months in the study by Zhu et al.) [67–69]. The use of drug-eluting stents, namely, with paclitaxel, had not shown expressive benefits [70].

The use of bilateral versus unilateral SEMS in the proximal MBO is an issue not yet resolved. Despite the better cumulative patency demonstrated in the studies, the complication and survival rates do not seem to improve in bilateral drainage, although the physiologic mechanism that would lead to a better outcome seems plausible [71–73].

Altogether it is not yet possible to state the optimal choice for palliative SEMS in MBO. Hence, each case has to be assessed individually and evaluated regarding the pros and cons. Novel products and techniques are promising but lacking in RCTs in favor of certain specific SEMS.

3.4. Radiofrequency Ablation. There are several papers in recent years demonstrating a good outcome in patients submitted to radiofrequency ablation (RFA) after the placement of a SEMS (occluded SEMS) or before its placement [74–76]. It is usually preferred over photodynamic therapy due to its complications [77–79]. Intraductal RFA can be performed either endoscopically or percutaneously through the insertion of a specific catheter that delivers heat energy directly to neoplastic tissues to achieve tumor necrosis and to prolong biliary patency. This procedure has a local effect and is not intended to be curative.

Despite its promising results, it is an experimental therapy that just a handful of centres have at disposal. There is still much research to be done before we can reach a consensus regarding how, when, and where this new technique should be used.

3.5. EUS. EUS assists in accessing the biliary tract via transgastric or transduodenal routes and is an option in cases where transpapillary route is inaccessible by ERCP. It is usually performed with a sectorial echoendoscope which identifies the hepatic ducts or the bile duct. The duct is punctured and a guidewire is placed, to guide the SEMS through the gastric or duodenal wall. Alternatively, EUS can also be used to exteriorize the guidewire through the papillae to guide a usually placed SEMS through ERCP in the so-called *rendezvous* technique. Although these state-of-the-art techniques are exciting, more studies are needed to confirm their efficacy and security compared with the percutaneous option when the transpapillary ERCP drainage is not possible.

Therefore, it is mainly an option in cases of failed transpapillary endoscopic drainage, with the advantage of maintaining physiologic bile flow through the gastrointestinal tract and having better comfort to the patient as internal drainage [80, 81].

4. Conclusions

In operable cases, routine preoperative stents shall not be placed unless the patient is cholangitic, there is delay in surgery, or intense jaundice is present. More research is needed to clarify the benefits of PTBD in proximal tumors and the cutoff level of bilirubin. Most of the studies used PS for PTBD, with just a few studies examining the role of SEMS. Therefore more data regarding SEMS for PBD is necessary to have a definitive answer.

For inoperable cases, surgery should be avoided and transpapillary stenting after sphincterotomy should be preferable over the percutaneous drainage approach. The use of PS for MBO has no demonstrated benefit over SEMS and should not be used, since new modalities of chemotherapy for metastatic patients, either with pancreatic adenocarcinoma or with cholangiocarcinoma, surpass 6 months of mean overall survival. In inaccessible transpapillary cases, EUS-guided drainage is still an option over the percutaneous approach. Among the types of SEMS, there is no significant difference between their uses and their indication should be individualized. The concurrent use of SEMS with radioisotopes, brachytherapy, and radiofrequency ablation shows promising results.

Conflict of Interests

All the authors declare that they have no competing interests.

References

[1] P. T. Roughneen, R. Didlake, S. C. Kumar, B. D. Kahan, and B. J. Rowlands, "Enhancement of heterotopic cardiac allograft survival by experimental biliary ligation," *Transplantation*, vol. 43, no. 3, pp. 437–438, 1987.

[2] M. Treglia-Dal Lago, J. Jukemura, M. C. C. Machado, J. E. M. da Cunha, and J. A. M. Barbuto, "Phagocytosis and production of H_2O_2 by human peripheral blood mononuclear cells from patients with obstructive jaundice," *Pancreatology*, vol. 6, no. 4, pp. 273–278, 2006.

[3] N. Kawarabayashi, S. Seki, K. Hatsuse et al., "Immunosuppression in the livers of mice with obstructive jaundice participates in their susceptibility to bacterial infection and tumor metastasis," *Shock*, vol. 33, no. 5, pp. 500–506, 2010.

[4] S. C. Katz, K. Ryan, N. Ahmed et al., "Obstructive jaundice expands intrahepatic regulatory T cells, which impair liver T lymphocyte function but modulate liver cholestasis and fibrosis," *The Journal of Immunology*, vol. 187, no. 3, pp. 1150–1156, 2011.

[5] D. B. Evans, M. B. Farnell, K. D. Lillemoe, C. Vollmer Jr., S. M. Strasberg, and R. D. Schulick, "Surgical treatment of resectable and borderline resectable pancreas cancer: expert consensus statement," *Annals of Surgical Oncology*, vol. 16, no. 7, pp. 1736–1744, 2009.

[6] R. Siegel, J. Ma, Z. Zou, and A. Jemal, "Cancer statistics, 2014," *CA: A Cancer Journal for Clinicians*, vol. 64, no. 1, pp. 9–29, 2014.

[7] Y. Reisman, C. H. Gips, S. M. Lavelle, and J. H. Wilson, "Clinical presentation of (subclinical) jaundice—the Euricterus project in The Netherlands. United Dutch Hospitals and Euricterus Project Management Group," *Hepatogastroenterology*, vol. 43, no. 11, pp. 1190–1195, 1996.

[8] M. T. Carriaga and D. E. Henson, "Liver, gallbladder, extrahepatic bile ducts, and pancreas," *Cancer*, vol. 75, no. 1, pp. 171–190, 1995.

[9] G. Parasher and J. G. Lee, "The role of ERCP in pancreatobiliary malignancies," *Advanced Digestive Endoscopy: ERCP*, vol. 6, pp. 120–141, 2006.

[10] A. M. van Berkel, P. Fockens, and M. J. Bruno, "Palliation of malignant pancreatobiliary obstruction," in *Clinical Gastrointestinal Endoscopy*, vol. 54, pp. 821–837, Saunders, Philadelphia, Pa, USA, 2005.

[11] D. P. Ryan, T. S. Hong, and N. Bardeesy, "Pancreatic adenocarcinoma," *The New England Journal of Medicine*, vol. 371, no. 11, pp. 1039–1049, 2014.

[12] E. C. Burke, W. R. Jarnagin, S. N. Hochwald, P. W. T. Pisters, Y. Fong, and L. H. Blumgart, "Hilar cholangiocarcinoma: patterns of spread, the importance of hepatic resection for curative operation, and a prosurgical clinical staging system," *Annals of Surgery*, vol. 228, no. 3, pp. 385–394, 1998.

[13] J. Albores-Saavedra, A. M. Schwartz, K. Batich, and D. E. Henson, "Cancers of the ampulla of vater: demographics, morphology, and survival based on 5,625 cases from the SEER program," *Journal of Surgical Oncology*, vol. 100, no. 7, pp. 598–605, 2009.

[14] http://www.inca.gov.br/.

[15] A. B. Ballinger, M. McHugh, S. M. Catnach, E. M. Alstead, and M. L. Clark, "Symptom relief and quality of life after stenting for malignant bile duct obstruction," *Gut*, vol. 35, no. 4, pp. 467–470, 1994.

[16] N. S. Abraham, J. S. Barkun, and A. N. Barkun, "Palliation of malignant biliary obstruction: a prospective trial examining impact on quality of life," *Gastrointestinal Endoscopy*, vol. 56, no. 6, pp. 835–841, 2002.

[17] A. Sauvanet, J. M. Boher, F. Paye et al., "Severe jaundice increases early severe morbidity and decreases long-term survival after pancreaticoduodenectomy for pancreatic adenocarcinoma," *Journal of the American College of Surgeons*, vol. 221, no. 2, pp. 380–389, 2015.

[18] D. Bonnel, T. André, B. Mader, J.-F. Lefebvre, E. Bensoussan, and C. Liguory, "Malignant biliary obstruction, general review and clinical practice," *Bulletin du Cancer*, vol. 100, no. 5, pp. 443–452, 2013.

[19] J. Deviere, M. Baize, M. Gelin et al., "Treatment of cancer of the head of the pancreas. Surgery and/or endoscopic prostheses," *Acta Gastro-Enterologica Belgica*, vol. 50, no. 1, pp. 137–146, 1987.

[20] A. Sadeghi, M. Mohamadnejad, F. Islami et al., "Diagnostic yield of EUS-guided FNA for malignant biliary stricture: a systematic review and meta-analysis," *Gastrointestinal Endoscopy*, vol. 83, no. 2, pp. 290–298.e1, 2016.

[21] M. D'Onofrio, R. De Robertis, E. Barbi et al., "Ultrasound-guided percutaneous fine-needle aspiration of solid pancreatic neoplasms: 10-year experience with more than 2,000 cases and a review of the literature," *European Radiology*, pp. 1–7, 2015.

[22] C. J. Tyng, M. F. Almeida, P. N. Barbosa et al., "Computed tomography-guided percutaneous core needle biopsy in pancreatic tumor diagnosis," *World Journal of Gastroenterology*, vol. 21, no. 12, pp. 3579–3586, 2015.

[23] I. Chen, T. Lorentzen, D. Linnemann et al., "Seeding after ultrasound-guided percutaneous biopsy of liver metastases in patients with colorectal or breast cancer," *Acta Oncologica*, 2015.

[24] A. Tringali, A. Lemmers, V. Meves et al., "Intraductal biliopancreatic imaging: European Society of Gastrointestinal Endoscopy (ESGE) technology review," *Endoscopy*, vol. 47, no. 8, pp. 739–753, 2015.

[25] J.-M. Dumonceau, A. Tringali, D. Blero et al., "Biliary stenting: indications, choice of stents and results: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline," *Endoscopy*, vol. 44, no. 3, pp. 277–298, 2012.

[26] Y. Fang, K. S. Gurusamy, Q. Wang et al., "Pre-operative biliary drainage for obstructive jaundice," *Cochrane Database of Systematic Reviews*, vol. 9, Article ID CD005444, 2012.

[27] C. Haapamäki, H. Seppänen, M. Udd et al., "Preoperative biliary decompression preceding pancreaticoduodenectomy with plastic or self-expandable metallic stent," *Scandinavian Journal of Surgery*, vol. 104, no. 2, pp. 79–85, 2015.

[28] J. A. Tol, J. E. van Hooft, R. Timmer et al., "Metal or plastic stents for preoperative biliary drainage in resectable pancreatic cancer," *Gut*, 2015.

[29] O. Farges, J. M. Regimbeau, D. Fuks et al., "Multicentre European study of preoperative biliary drainage for hilar cholangiocarcinoma," *British Journal of Surgery*, vol. 100, no. 2, pp. 274–283, 2013.

[30] A. Coss and M. F. Byrne, "Preoperative biliary drainage in malignant obstruction: indications, techniques, and the debate over risk," *Current Gastroenterology Reports*, vol. 11, no. 2, pp. 145–149, 2009.

[31] Y. Takahashi, M. Nagino, H. Nishio, T. Ebata, T. Igami, and Y. Nimura, "Percutaneous transhepatic biliary drainage catheter tract recurrence in cholangiocarcinoma," *British Journal of Surgery*, vol. 97, no. 12, pp. 1860–1866, 2010.

[32] J. K. Wiggers, B. G. Koerkamp, R. J. Coelen et al., "Preoperative biliary drainage in perihilar cholangiocarcinoma: identifying patients who require percutaneous drainage after failed endoscopic drainage," *Endoscopy*, vol. 47, no. 12, pp. 1124–1131, 2015.

[33] C. Xu, P.-H. Lv, X.-E. Huang, S.-X. Wang, L. Sun, and F.-A. Wang, "Analysis of different ways of drainage for obstructive jaundice caused by hilar cholangiocarcinoma," *Asian Pacific Journal of Cancer Prevention*, vol. 15, no. 14, pp. 5617–5620, 2014.

[34] P. J. Cui, J. Yao, Y. J. Zhao, H. Z. Han, and J. Yang, "Biliary stenting with or without sphincterotomy for malignant biliary obstruction: a meta-analysis," *World Journal of Gastroenterology*, vol. 20, no. 38, pp. 14033–14039, 2014.

[35] J.-H. Jo and B.-H. Park, "Suprapapillary versus transpapillary stent placement for malignant biliary obstruction: which is better?" *Journal of Vascular and Interventional Radiology*, vol. 26, no. 4, pp. 573–582, 2015.

[36] C. S. Ho and A. E. Warkentin, "Evidence-based decompression in malignant biliary obstruction," *Korean Journal of Radiology*, vol. 13, supplement 1, pp. S56–S61, 2012.

[37] M. Distler, S. Kersting, F. Rückert et al., "Palliative treatment of obstructive jaundice in patients with carcinoma of the pancreatic head or distal biliary tree. Endoscopic stent placement vs. hepaticojejunostomy," *Journal of the Pancreas*, vol. 11, no. 6, pp. 568–574, 2010.

[38] J. Śmigielski, J. Hołyński, M. Kococik et al., "Paliative procedures in cholangiocarcinomas—experience of 5 centers," *Polski Merkuriusz Lekarski*, vol. 26, no. 155, pp. 416–419, 2009.

[39] S. B. Edge, D. R. Byrd, C. C. Compton, A. G. Fritz, F. L. Greene, and A. Trotti, *AJCC (American Joint Committee on Cancer) Cancer Staging Manual*, Springer, New York, NY, USA, 7th edition, 2010.

[40] M. Arvanitakis and J. Devière, "Endoscopic retrograde cholangiopancreatography," *Endoscopy*, vol. 36, no. 10, pp. 855–859, 2004.

[41] H. Baume, M. Huguier, and J. M. Fabre, "Palliative treatment of cancers of the headof the pancreas. Surgery versus endoscopy," *Annales de Chirurgie*, vol. 49, no. 2, pp. 110–115, 1995.

[42] S. L. Alves de Lima, F. A. C. Bustamante, E. G. Hourneaux de Moura et al., "Endoscopic palliative treatment versus surgical bypass in malignant low bile duct obstruction: a systematic review and meta-analysis," *International Journal of Hepatobiliary and Pancreatic Diseases*, vol. 5, pp. 35–46, 2015.

[43] D. Walter, P. G. Van Boeckel, M. Groenen et al., "606 Metal stent placement is cost-effective for palliation of malignant common bile duct obstruction: a randomized controlled trial," *Gastrointestinal Endoscopy*, vol. 79, no. 5, supplement, pp. AB157–AB158, 2014.

[44] T. Mukai, I. Yasuda, M. Nakashima et al., "Metallic stents are more efficacious than plastic stents in unresectable malignant hilar biliary strictures: a randomized controlled trial," *Journal of Hepato-Biliary-Pancreatic Sciences*, vol. 20, no. 2, pp. 214–222, 2013.

[45] H. Isayama, I. Yasuda, S. Ryozawa et al., "Results of a Japanese multicenter, randomized trial of endoscopic stenting for non-resectable pancreatic head cancer (JM-test): covered Wallstent *vs* DoubleLayer stent," *Journal of Digestive Endoscopy*, vol. 23, no. 4, pp. 310–315, 2011.

[46] M. Bernon, J. Shaw, J. Krige, and P. Bornman, "Malignant biliary obstruction: a prospective randomised trial comparing plastic and metal stents for palliation of symptomatic jaundice," *HPB*, vol. 13, pp. 139–145, 2011.

[47] C. Soderlund and S. Linder, "Covered metal versus plastic stents for malignant common bile duct stenosis: a prospective, randomized, controlled trial," *Gastrointestinal Endoscopy*, vol. 63, no. 7, pp. 986–995, 2006.

[48] P. Katsinelos, D. Paikos, J. Kountouras et al., "Tannenbaum and metal stents in the palliative treatment of malignant distal bile duct obstruction: a comparative study of patency and cost effectiveness," *Surgical Endoscopy and Other Interventional Techniques*, vol. 20, no. 10, pp. 1587–1593, 2006.

[49] M. Kaassis, J. Boyer, R. Dumas et al., "Plastic or metal stents for malignant stricture of the common bile duct? Results of a randomized prospective study," *Gastrointestinal Endoscopy*, vol. 57, no. 2, pp. 178–182, 2003.

[50] P. H. P. Davids, A. K. Groen, E. A. J. Rauws, G. N. J. Tytgat, and K. Huibregtse, "Randomised trial of self-expanding metal stents versus polyethylene stents for distal malignant biliary obstruction," *The Lancet*, vol. 340, no. 8834-8835, pp. 1488–1492, 1992.

[51] K. Knyrim, H. J. Wagner, J. Pausch, and N. Vakil, "A prospective, randomized, controlled trial of metal stents for malignant obstruction of the common bile duct," *Endoscopy*, vol. 25, no. 3, pp. 207–212, 1993.

[52] H.-J. Wagner, K. Knyrim, N. Vakil, and K. J. Klose, "Plastic endoprostheses versus metal stents in the palliative treatment of malignant hilar biliary obstruction. A prospective and randomized trial," *Endoscopy*, vol. 25, no. 3, pp. 213–218, 1993.

[53] F. Prat, O. Chapat, B. Ducot et al., "A randomized trial of endoscopic drainage methods for inoperable malignant strictures of the common bile duct," *Gastrointestinal Endoscopy*, vol. 47, no. 1, pp. 1–7, 1998.

[54] P. L. Moses, K. M. Alnaamani, A. N. Barkun et al., "Randomized trial in malignant biliary obstruction: plastic *vs* partially covered metal stents," *World Journal of Gastroenterology*, vol. 19, no. 46, pp. 8638–8646, 2013.

[55] A. Sangchan, W. Kongkasame, A. Pugkhem, K. Jenwitheesuk, and P. Mairiang, "Efficacy of metal and plastic stents in unresectable complex hilar cholangiocarcinoma: a randomized controlled trial," *Gastrointestinal Endoscopy*, vol. 76, no. 1, pp. 93–99, 2012.

[56] L. Z. Pu, E. G. H. de Moura, W. M. Bernardo et al., "Endoscopic stenting for inoperable malignant biliary obstruction: a systematic review and meta-analysis," *World Journal of Gastroenterology*, vol. 21, no. 47, pp. 13374–13385, 2015.

[57] H. S. Kim, H. Y. Kim, D. Y. Zang et al., "Phase II study of gemcitabine and S-1 combination chemotherapy in patients with metastatic biliary tract cancer," *Cancer Chemotherapy and Pharmacology*, vol. 75, no. 4, pp. 711–718, 2015.

[58] J. Harder, G. Ihorst, V. Heinemann et al., "Multicentre phase II trial of trastuzumab and capecitabine in patients with HER2 overexpressing metastatic pancreatic cancer," *British Journal of Cancer*, vol. 106, no. 6, pp. 1033–1038, 2012.

[59] S. J. Lee, M. D. Kim, M. S. Lee et al., "Comparison of the efficacy of covered versus uncovered metallic stents in treating inoperable malignant common bile duct obstruction: a randomized trial," *Journal of Vascular and Interventional Radiology*, vol. 25, no. 12, pp. 1912–1920, 2014.

[60] Y. N. Lee, J. H. Moon, H. J. Choi et al., "Effectiveness of a newly designed anti-reflux valve metal stent to reduce duodenobiliary reflux in patients with unresectable distal malignant biliary obstruction: a randomized controlled pilot study (with videos)," *Gastrointestinal Endoscopy*, vol. 83, no. 2, pp. 404–412, 2016.

[61] C. Soderlund, S. Linder, P. E. Bergenzaun et al., "Nitinol versus steel partially covered self-expandable metal stent for malignant distal biliary obstruction: a randomized trial," *Endoscopy*, vol. 46, no. 11, pp. 941–948, 2014.

[62] J. H. Lee, S. G. Krishna, A. Singh et al., "Comparison of the utility of covered metal stents versus uncovered metal stents in the management of malignant biliary strictures in 749 patients," *Gastrointestinal Endoscopy*, vol. 78, no. 2, pp. 312–324, 2013.

[63] M. J. Yang, J. H. Kim, B. M. Yoo et al., "Partially covered versus uncovered self-expandable nitinol stents with anti-migration properties for the palliation of malignant distal biliary obstruction: a randomized controlled trial," *Scandinavian Journal of Gastroenterology*, vol. 50, no. 12, pp. 1490–1499, 2015.

[64] Z. Yang, Q. Wu, F. Wang, X. Ye, X. Qi, and D. Fan, "A systematic review and meta-analysis of randomized trials and prospective studies comparing covered and bare self-expandable metal stents for the treatment of malignant obstruction in the digestive tract," *International Journal of Medical Sciences*, vol. 10, no. 7, pp. 825–835, 2013.

[65] H. Moole, S. Dhillon, F.-H. Volmar, M. D. Cashman, M. L. Bechtold, and S. R. Puli, "Mo1378 Is there a survival and morbidity benefit of covered over uncovered metal stents in malignant biliary strictures? A meta-analysis and systematic review," *Gastrointestinal Endoscopy*, vol. 81, no. 5, supplement, p. AB399, 2015.

[66] Y. N. Lee, J. H. Moon, H. J. Choi et al., "Effectiveness of a newly designed antireflux valve metal stent to reduce duodenobiliary reflux in patients with unresectable distal malignant biliary obstruction: a randomized, controlled pilot study (with videos)," *Gastrointestinal Endoscopy*, vol. 83, no. 2, pp. 404–412, 2016.

[67] H.-D. Zhu, J.-H. Guo, G.-Y. Zhu et al., "A novel biliary stent loaded with ^{125}I seeds in patients with malignant biliary obstruction: preliminary results versus a conventional biliary stent," *Journal of Hepatology*, vol. 56, no. 5, pp. 1104–1111, 2012.

[68] W. Zhang, Z. Q. Yang, H. B. Shi, S. Liu, W. Z. Zhou, and L. B. Zhao, "Placement of ^{125}I seed strands and stents for a type IV Klatskin tumor," *World Journal of Gastroenterology*, vol. 21, no. 1, pp. 373–376, 2015.

[69] G. C. Mattiucci, R. Autorino, A. Tringali et al., "A Phase I study of high-dose-rate intraluminal brachytherapy as palliative treatment in extrahepatic biliary tract cancer," *Brachytherapy*, vol. 14, no. 3, pp. 401–404, 2015.

[70] T. J. Song, S. S. Lee, S. C. Yun et al., "Paclitaxel-eluting covered metal stents versus covered metal stents for distal malignant biliary obstruction: a prospective comparative pilot study," *Gastrointestinal Endoscopy*, vol. 73, no. 4, pp. 727–733, 2011.

[71] M. Li, W. Wu, Z. Yin, and G. Han, "Unilateral versus bilateral biliary drainage for malignant hilar obstruction: a systematic review and meta-analysis," *Zhonghua Gan Zang Bing Za Zhi*, vol. 23, no. 2, pp. 118–123, 2015 (Chinese).

[72] I. Naitoh, H. Ohara, T. Nakazawa et al., "Unilateral versus bilateral endoscopic metal stenting for malignant hilar biliary obstruction," *Journal of Gastroenterology and Hepatology*, vol. 24, no. 4, pp. 552–557, 2009.

[73] G. D. De Palma, G. Galloro, S. Siciliano, P. Iovino, and C. Catanzano, "Unilateral versus bilateral endoscopic hepatic duct drainage in patients with malignant hilar biliary obstruction: results of a prospective, randomized, and controlled study," *Gastrointestinal Endoscopy*, vol. 53, no. 6, pp. 547–553, 2001.

[74] R. Z. Sharaiha, A. Sethi, K. R. Weaver et al., "Impact of radiofrequency ablation on malignant biliary strictures: results of a collaborative registry," *Digestive Diseases and Sciences*, vol. 60, no. 7, pp. 2164–2169, 2015.

[75] T.-T. Wu, H.-C. Li, W.-M. Li et al., "Percutaneous intraluminal radiofrequency ablation for malignant extrahepatic biliary

obstruction: a safe and feasible method," *Digestive Diseases and Sciences*, vol. 60, no. 7, pp. 2158–2163, 2015.

[76] X. H. Duan, Y. L. Wang, X. W. Han et al., "Intraductal radiofrequency ablation followed by locoregional tumor treatments for treating occluded biliary stents in non-resectable malignant biliary obstruction: a single-institution experience," *PLoS ONE*, vol. 10, no. 8, Article ID e0134857, 2015.

[77] M. E. J. Ortner, K. Caca, F. Berr et al., "Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study," *Gastroenterology*, vol. 125, no. 5, pp. 1355–1363, 2003.

[78] S. P. Pereira, L. Ayaru, A. Rogowska, A. Mosse, A. R. W. Hatfield, and S. G. Bown, "Photodynamic therapy of malignant biliary strictures using meso-tetrahydroxyphenylchlorin," *European Journal of Gastroenterology and Hepatology*, vol. 19, no. 6, pp. 479–485, 2007.

[79] T. Zoepf, R. Jakobs, J. C. Arnold, D. Apel, and J. F. Riemann, "Palliation of nonresectable bile duct cancer: Improved survival after photodynamic therapy," *American Journal of Gastroenterology*, vol. 100, no. 11, pp. 2426–2430, 2005.

[80] S. Brückner, A. Arlt, and J. Hampe, "Endoscopic ultrasound-guided biliary drainage using a lumen-apposing self-expanding metal stent: a case series," *Endoscopy*, vol. 47, no. 9, pp. 858–861, 2015.

[81] L. Poincloux, O. Rouquette, E. Buc et al., "Endoscopic ultrasound-guided biliary drainage after failed ERCP: cumulative experience of 101 procedures at a single center," *Endoscopy*, vol. 47, no. 09, pp. 794–801, 2015.

Hindawi Publishing Corporation
Gastroenterology Research and Practice
Volume 2016, Article ID 8732521, 13 pages
http://dx.doi.org/10.1155/2016/8732521

Research Article

Extensive Use of Interventional Therapies Improves Survival in Unresectable or Recurrent Intrahepatic Cholangiocarcinoma

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Received 12 October 2015; Accepted 20 December 2015

Academic Editor: Mohamad H. Imam

Aim. To assess the outcomes of patients with unresectable intrahepatic cholangiocellular carcinoma (ICC) treated by a tailored therapeutic approach, combining systemic with advanced image-guided local or locoregional therapies. *Materials and Methods*. Treatment followed an algorithm established by a multidisciplinary GI-tumor team. Treatment options comprised ablation (RFA, CT-guided brachytherapy) or locoregional techniques (TACE, radioembolization, i.a. chemotherapy). *Results*. Median survival was 33.1 months from time of diagnosis and 16.0 months from first therapy. UICC stage analysis showed a median survival of 15.9 months for stage I, 9 months for IIIa, 18.4 months for IIIc, and 13 months for IV. Only the number of lesions, baseline serum CEA and serum CA19-9, and objective response (RECIST) were independently associated with survival. Extrahepatic metastases had no influence. *Conclusion*. Patients with unresectable ICC may benefit from hepatic tumor control provided by local or locoregional therapies. Future prospective study formats should focus on supplementing systemic therapy by classes of interventions ("toolbox") rather than specific techniques, that is, local ablation leading to complete tumor destruction (such as RFA) or locoregional treatment leading to partial remission (such as radioembolization). This trial is registered with German Clinical Trials Registry (Deutsche Register Klinischer Studien), DRKS-ID: DRKS00006237.

1. Introduction

Peripheral or intrahepatic cholangiocellular carcinoma (ICC) is a rare neoplasm. However, its incidence and mortality have been reported to be increasing worldwide [1]. Prognosis is poor, with a 5-year survival below 5%, including patients who do undergo tumor resection. However, surgical treatment currently represents the only potentially curative therapy. Unfortunately only 20% of patients are eligible for resection because of disease spread, anatomic location, inadequate hepatic reserve, or limiting comorbidities [2–5].

Median survival for patients with untreated unresectable ICC has been reported as 3–6 months [5, 6]. Furthermore, systemic intravenous (i.v.) chemotherapy (ivCTX) has only limited benefit. Although modern chemotherapy regimens have improved survival considerably in recent years, median survival is still less than one year for, for example, gemcitabine plus cisplatin [7].

Several palliative therapeutic options exist for patients with unresectable ICC. The goals of palliative therapy are to control local tumor growth, to relieve symptoms, and to improve and preserve quality of life. Thus, local-ablative

treatment options are gaining attention, as results from studies analyzing radiofrequency ablation (RFA) and ^{90}Y-radioembolization (RE), high dose rate brachytherapy (HDR-BT), intra-arterial chemotherapy (iaCTX), and transarterial chemoembolization (TACE) have been encouraging [8–12].

However, most of these studies included patients with intrahepatic and extrahepatic cholangiocarcinoma or gallbladder cancer and involved only a small number of patients, so that definitive conclusions are sometimes difficult to draw.

Since 2006, we have treated patients with unresectable or recurrent ICC by different local therapies (alone or in combination) according to a therapy algorithm that was established after thorough discussion in a multidisciplinary team (GI board) involving surgeons, gastroenterologists, medical oncologists, and interventional radiologists. Data from these patients treated according to this algorithm were prospectively collected in an institutional database.

In the study described herein we present the clinical outcomes of this patient-tailored therapeutic approach, combining systemic and image-guided local or locoregional therapies for the treatment of intrahepatic cholangiocarcinoma in nonsurgical candidates.

2. Materials and Methods

This study was compliant with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by our Institutional Review Board (positive vote assigned by "Ethikkommission der Medizinischen Fakultät der Otto-von-Guericke-Universität Magdeburg" at 7-16-2013); written informed consent to scientific use of data was obtained before therapy. All clinical data were obtained from the prospectively maintained institutional ICC database.

The study was registered at DRKS (Deutsche Register Klinischer Studien DRKS00006237).

2.1. Patients. From March 2006 to June 2012 (last follow-up performed in March 2013), 75 consecutive patients with unresectable ICC were referred to our multidisciplinary GI board and received treatment recommendations with local or locoregional treatments often supplementary to systemic treatments. All of these patients were not surgical candidates due to advanced tumor stage, comorbidities, or refused resection. From this cohort, 20 patients were excluded from analysis: 10 were lost to follow-up within the first two months (most of them initially referred from distant centers) and 10 presented with a secondary malignoma (3 of those with an additional extrahepatic cholangiocellular carcinoma, i.e., Klatskin tumor). Thus, 55 patients were analyzed. Patient and tumor characteristics at the time of first local or locoregional therapy are summarized in Table 1.

Palliative treatment options were part of the aforementioned multidisciplinary treatment algorithm. The algorithm is outlined in detail in Figure 1. Image-guided techniques comprised RFA (radiofrequency ablation), TACE (conventional chemoembolization), HDR-BT (CT-guided interstitial high dose rate brachytherapy), RE (^{90}Y-radioembolization), iaCTX (intra-arterial chemotherapy), and ivCTX (intravenous chemotherapy).

Factors guiding the treatment allocation included stage and specific morphological properties of the disease (tumor size, number of lesions, and preexisting extrahepatic metastases) as well as liver function and performance status.

All 55 patients analyzed have been treated with at least one local or locoregional treatment option at our clinic. Patients were reassessed with clinical examination and CT or MR imaging every 3 months thereafter. According to that restaging patients were entered in the treatment algorithm again if disease progression was present. As a consequence, 37 out of 55 patients received one type of ablative or locoregional therapy, whereas another 18 patients received a combination of additional image-guided therapies. With 21 patients presenting after previous, often multiple chemotherapy lines, 16 patients received systemic treatments after the first local/locoregional intervention. All treatment details after inclusion as well as tumor-targeted prior treatments are outlined in detail in Table 1.

2.2. Evaluation and Staging. Diagnosis of ICC was based on biopsy. Pretreatment assessment consisted of demographics, presence or absence of cirrhosis, biliary obstruction and portal invasion, extrahepatic metastases, and prior treatments. Diagnostic imaging was performed by magnetic-resonance imaging (MRI) and/or triphasic computerized tomography (CT).

Staging was performed at the time of first diagnosis as baseline staging and again at the time of the first interventional therapy at our institution by the TNM classification adapted from the 6th edition of the staging manual of the UICC/AJCC [13]. Lymph nodes were considered to be metastatic when they were larger than 1 cm in short-axis diameter [14].

The treatment algorithm groups patients according to six potential treatments (Figure 1). Patients with single tumors ($n \leq 4$) received HDR-BT, TACE, or RFA in the absence of portal vein thrombosis (PVT). In case of PVT, only HDR-BT or RFA were applicable. Concomitant chemotherapy was recommended in patients with biologically aggressive tumors (disease free interval < 12 months) specifically in chemotherapy-naïve patients. In patients with biologically favorable tumors with disease free interval ≥ 12 months, an ECOG > 1, and/or previous chemotherapies further chemotherapies immediately after complete ablative or locoregional treatment were not recommended.

Patients with multinodular ($n > 4$) or diffuse disease received radioembolization or iaCTX with 5-fluorouracil/leucovorin (5-FU/LV) when bilirubin was less than 30 μmol/L. If bilirubin was 30–50 μmol/L, iaCTX was preferred alone or in combination with HDR-BT or RFA (depending on the likelihood for reliable, technically safe complete tumor destruction). Patients with bilirubin above 50 μmol/L and those with diffuse peritoneal carcinomatosis were not eligible for any local-ablative or locoregional therapy and received ivCTX or best supportive care only. All treatment recommendations were issued by the multidisciplinary gastrointestinal oncology team in consensus.

Table 1: Patients' characteristics.

Demographics and disease history		%/(range)
Total *N*	55	100%
Sex		
Male	28	50.9%
Female	27	49.1%
Age, year		
Median	67.3	(34.0–82.6)
≤65	25	45.5%
>65	30	54.5%
Months from diagnosis to 1st therapy		
Median	10	(0.8–64.4)
Karnofsky index, $n = 47$		
Median	70	(60–100)
60	9	16.4%
70	13	23.4%
80	14	25.6%
90	17	31.0%
100	2	3.6%
ECOG index, $n = 47$		
Median	1	(0–2)
0	19	34.6%
1	27	49.0%
2	9	16.4%
Prior liver-directed treatment (*n*)		
Any	21	38.2%
Resection	15	27.3%
Intraoperative RFA	3	5.5%
TACE	2	3.6%
RFA	1	1.8%
Prior chemotherapy (*n*)		
Yes	21	38.2%
No	34	61.8%
Prior chemotherapy lines (*n*)		
One	17	30.9%
Two	2	3.6%
>two	2	3.6%
Median	1	(1–5)
Prior chemotherapy agents (*n*)		
Gemcitabine	19	34.5%
Oxaliplatin	12	21.8%
Capecitabine	8	14.5%
5-FU/FA	4	7.3%
Cisplatin	3	5.5%
Others*	9	16.4%
T-stage (*n*)		
T1	21	38.2%
T2	12	21.8%
T3	21	38.2%
T4	1	1.8%

Table 1: Continued.

Demographics and disease history		%/(range)
Overall tumor stage (UICC**) (*n*) at first diagnosis		
Stage I	17	30.9%
Stage II	3	5.5%
Stage IIIa	3	5.5%
Stage IIIb	0	0%
Stage IIIc	21	38.2%
Stage IV	5	9.1%
No information available	6	10.9%
Overall tumor stage (UICC**) (*n*) at first local therapy in Magdeburg		
Stage I	11	20.0%
Stage II	5	9.1%
Stage IIIa	3	5.5%
Stage IIIb	0	0%
Stage IIIc	22	40.0%
Stage IV	14	25.5%
CEA		
Median, range [ng/mL]	2.6	(0.3–391.7)
Elevated, >3.4 ng/mL (*n*)	23	41.8%
Not elevated (*n*)	32	58.2%
CA 19–9		
Median, range [U/mL]	66	(0.6–72.9)
Elevated, >39.9 U/mL (*n*)	34	61.8%
Not elevated (*n*)	21	38.2%
Tumor load		
Median, range (%)	8	(2–80)
Tumor size		
Median, range (mm)	45	(14–189)
Extent of disease (*n*)		
Bilobar	32	58.2%
Unilobar	23	41.8%
Extrahepatic metastases (*n*)		
All	36	65.5%
Lymph node metastases	32	58.2%
Peritoneal metastases	8	14.5%
Pulmonary metastases	5	9.1%
Bone metastases	2	3.6%
Concomitant liver disease (*n*)		
Vascular infiltration	21	38.2%
Cirrhosis	20	36.4%
Biliary obstruction	18	32.7%
Portal vein thrombosis	10	18.2%
Ascites	7	12.7%
Therapies and combinations of therapies (*n*)		
HDR-BT	19	34.5%
RE	5	9.1%
TACE	2	3.6%
RFA	1	1.8%
HDR-BT & ivCTX	11	20.0%
HDR-BT & iaCTX	6	10.9%
HDR-BT & RE	3	5.5%
HDR-BT & RFA	2	3.6%

Table 1: Continued.

Demographics and disease history		%/(range)
HDR-BT & iaCTX & ivCTX	2	3.6%
HDR-BT & RE & ivCTX	2	3.6%
TACE & ivCTX	1	1.8%
RE & iaCTX	1	1.8%

*Irinotecan ($n = 1$), taxotere ($n = 1$), bevacizumab ($n = 1$), erlotinib ($n = 1$), mitomycin C ($n = 1$), cetuximab ($n = 2$), and sorafenib ($n = 2$).
**Acc. to UICC Edition 6, stage I disease is a solitary tumor without vascular involvement; stage II disease is a solitary tumor with vascular invasion or multiple tumors <5 cm; stage IIIa disease is multiple tumors >5 cm with or without vascular invasion; stage IIIb disease is perforation of the peritoneum or infiltration of adjacent organs; stage IIIc disease is any tumor with regional lymph node metastasis; and stage IV disease is any tumor with distant metastasis.

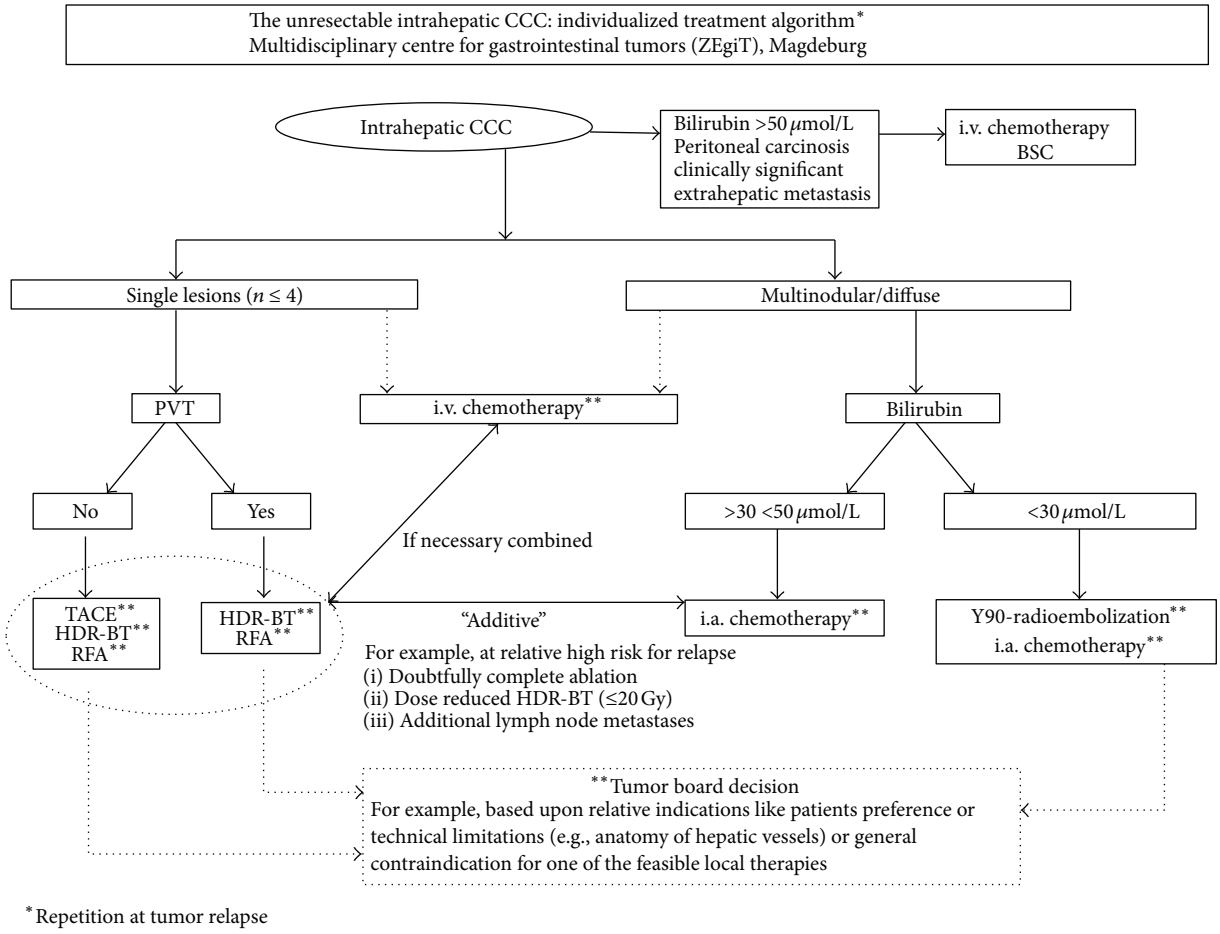

Figure 1: Algorithm for the treatment of intrahepatic cholangiocellular carcinoma. CCC, cholangiocellular carcinoma; HDR-BT, image-guided HDR brachytherapy; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; i.a., intra-arterial; i.v., intravenous; BSC, best supportive care; PVT, portal venous thrombosis.

Complications were classified following CTCAE v4.0, with minor (CTCAE Grades 1 and 2) or major complications (CTCAE Grades 3 and 4).

2.3. Local-Ablative Therapies

2.3.1. Radiofrequency Ablation (RFA). RFA is an ablative technique intending complete local tumor destruction. RFA was performed under CT or MRI guidance using a radiofrequency applicator, which can be expanded stepwise to cover an area of maximum diameter 5 cm and a 150 W RF generator (Starburst Semi-Flex; AngioDynamics, Mountain View, CA) [15, 16]. The RFA protocol was always completed according to the manufacturer's instructions; completeness of ablation was confirmed by MRI 24 hours after RFA.

2.3.2. Image-Guided HDR Brachytherapy (HDR-BT). The technique of HDR-BT has been described in detail elsewhere [9, 17]. As an ablative technique, its intention is complete and durable local tumor destruction. In brief, liver malignancies

are treated with high dose rates of iridium-192 in an afterloading technique after percutaneous positioning of the brachytherapy catheters under CT or MRI control. The prescribed minimum dose for the clinical target volume is 20 Gy. Specifically in patients where RFA is not feasible owing to larger tumor sizes (>5 cm) or adjacent, potentially cooling structures such as larger vessels, HDR-BT is a useful option [18–20].

2.3.3. Radioembolization (RE) with Yttrium-90 Microspheres. Radioembolization with ^{90}Y-labeled resin microspheres has been shown to be effective in unresectable ICC and tumor metastases of the liver [21, 22]. Its intended effect was partial remission of diffuse hepatic tumor spread rather than complete tumor ablation.

The principle of RE is based on the dual blood supply of the liver from the portal vein and the hepatic artery, so delivery of the radioactive microspheres via the hepatic artery results in high dose local irradiation with only minor effects on normal liver tissue. All patients underwent pretreatment mesenteric angiography and ^{99}Tc-macroaggregated albumin scanning to minimize the risk of nontarget embolisation [19, 23]. A detailed account of the treatment protocol has been published previously [22]. The median dose was 1.63 GBq (range 0.9–2.55 GBq).

2.3.4. Transarterial Chemoembolization (TACE). The intended effect of TACE was partial remission of limited hepatic tumor spread beyond the technical capabilities of local ablation such as through RFA or CT-guided brachytherapy. TACE was conducted by standard techniques with an emulsion of doxorubicin and cisplatin in lipiodol (1 mL contains 0.5 mL lipiodol and 2.5 mg each of doxorubicin and cisplatin) until stasis in tumor feeding arteries was achieved. No additional embolization particles were administered. TACE was performed every 6 weeks. After three sessions tumor response was assessed by CT and/or MRI and, depending on outcome, TACE was either continued or interrupted [19, 24, 25].

2.3.5. Intra-Arterial Chemotherapy (iaCTX). iaCTX was performed on an outpatient basis. Chemotherapy was delivered through a microcatheter-port system into the hepatic artery, implanted via the common femoral artery as described elsewhere [26]. This method potentially decreases systemic side effects (e.g., nausea and vomiting) and may optimize the chemotoxic effects of the drugs in the hepatic malignancy [27, 28].

Intra-arterial chemotherapy consisted of daily infusions of fluorouracil (5-FU) 600 mg/mÂš and folinic acid 170 mg/mÂš on days 1–5, repeated on day 22.

Nine patients (16%) received a median of 6 cycles (range 4–23 cycles) of intra-arterial 5-FU chemotherapy.

2.3.6. Intravenous Chemotherapy (ivCTX). Lacking a well-defined therapeutic standard until 2010, various ivCTX regimens have been administered following protocols including monotherapy or combinations of cisplatin, gemcitabine, oxaliplatin, 5-FU/FA, and capecitabine [7, 29, 30]. Since 2010 the standard first-line therapy was gemcitabine combined with cisplatin [7]. In our study, sixteen patients received ivCTX in combination with their local therapy. The median number of chemotherapeutic cycles was 5 (range 1–12). Thirteen patients (24%) received one line of ivCTX, two (4%) received a second line, and one (2%) received a third line. Patients who had been treated with ivCTX only are not part of this analysis.

2.4. Follow-Up/Clinical Assessments. At imaging follow-up, usually every three months after the intervention, clinical assessment and laboratory tests (blood counts, liver function tests, and tumor markers (carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA))) were routinely performed.

Patients diagnosed with progressing ICC during follow-up were reassessed by the multidisciplinary treatment decision algorithm and treated again accordingly. Patients were followed until death or censored at the last known clinical follow-up.

2.5. Imaging Analysis. Patients were examined every three months by liver MRI using the liver-specific contrast agent gadoxetic acid (Gd-EOB-DTPA, Primovist, Bayer Healthcare, Berlin, Germany) or triphasic contrast-enhanced CT with iopremol 300 (Imeron 300, Bracco Imaging, SpA, Milan, Italy) of the abdomen. Every six months a chest X-ray was conducted and once a year a multislice CT of the thorax. Response was assessed applying the RECIST 1.1 criteria [31].

2.6. Statistical Analysis. Descriptive statistics were calculated for quantitative variables; frequency counts by category were calculated for qualitative variables; 95% confidence intervals are presented where appropriate. p values were considered significant if <0.05. The primary study endpoint was overall survival (estimated from the date of first interventional therapy at our institution and additionally from the date of first diagnosis), analyzed by the Kaplan-Meier method and compared between different groups by a log-rank test.

The following prognostic factors for influencing patient survival were evaluated: patient's age and sex, time interval from first diagnosis to first local therapy at our institution, performance status at the time of first local therapy at our institution (Karnofsky and ECOG), prior resection, prior chemotherapies, prior local therapies, tumor load, tumor number, tumor size and tumor stage (according to UICC), extrahepatic metastasis, vascular infiltration, portal vein invasion, biliary obstruction, ascites, cirrhosis, elevated tumor marker levels (CEA and CA 19-9), best response, and therapy-associated complications.

Several prognostic factors were grouped for analysis of differences in survival. These are listed below (Table 3).

Univariate and multivariate Cox regression analyses were performed to identify factors associated with the patients' survival. Only factors showing significance ($p < 0.05$) in the univariate model were included in the multivariate analysis.

Statistical analyses were performed with SPSS (version 21, IBM, Chicago, IL, USA).

Table 2: Treatment characteristics and cumulative toxicities analysis: only Grade 3-4 toxicities are reported (CTCAE version 4.0).

Treatment characteristics	HDR-BT	RE	RFA	TACE	ivCTX	iaCTX
Patients (*n*)	45	11	3	3	16	9
Karnofsky index, median (range)	80 (60–100)	80 (60–90)	90 (60–90)	70 (70)	70 (60–100)	90 (80–90)
ECOG index, median (range)	1 (0–2)	1 (0–2)	0 (0–2)	1 (1-1)	1 (0–2)	0 (0-1)
Number of days hospitalized, median (range)	4 (1–11)	4 (3–5)	5 (4–6)	4 (3–6)	0	0
Total number of treatments/chemotherapeutic cycles (*n*)	101	20	3	12	64	43
Median number of treatments/chemotherapeutic cycles per patient (range)	1 (1–5)	1 (1–4)	3 (1-1)	4 (3–5)	5 (1–12)	6 (4–23)
Median RE-dose delivered (GBq), median (range)	—	1.63 (0.9–2.55)	—	—	—	—
Best response	CR	PR	CR	PD	SD	PR
Adverse events acc. CTCAE (highest grade recorded)	3	2	2	1	3	2
Abscess (*n*)	1	—	—	—	—	—
Shivering* (*n*)	1	—	—	—	—	—
Hematoma subcapsular (*n*)	1	—	—	—	—	—
Anemia (*n*)	—	—	—	—	1	—
Thrombopenia (*n*)	—	—	—	—	1	—
Neutropenia (*n*)	—	—	—	—	1	—
Anorexia (*n*)	—	—	—	—	1	—
Fatigue (*n*)	—	—	—	—	2	—
Pain (*n*)	—	—	—	—	1	—
Diarrhea (*n*)	—	—	—	—	1	—
Rash (*n*)	—	—	—	—	1	—

Data are expressed as absolute number of events (*n*).
CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. CTCAE, common toxicity criteria of adverse events.
*Shivering due to radiation effects during HDR-BT with the need for abruption of the intervention.

3. Results

3.1. Patient Population. Table 1 summarizes the patient and tumor characteristics in the current study.

At the time of first interventional treatment, 58% of the patients suffered from bilobar tumor spread, the median tumor size was 45 mm, and 65% presented with extrahepatic metastasis (lymph node metastasis ($n = 32$), single peritoneal nodules ($n = 8$), and pulmonary ($n = 5$) and bone metastasis ($n = 2$)).

Forty-two patients (76%) underwent prior therapies before local intervention at our institution, 21 (38%) had undergone liver-directed therapy, and another 21 patients (38%) had received ivCTX.

3.2. Treatment Characteristics and Complication Rates. Treatment characteristics and Grade 3-4 treatment-related toxicities of all 55 patients are summarized in Table 2.

For 101 sessions of HDR brachytherapy, 3 (3%) Grade 3 events (no Grade 4) were reported. Of 16 patients who received ivCTX combined with a local therapy, 9 (56%) suffered from Grade 3 toxicities (no Grade 4). Patients receiving iaCTX, TACE, RE, or RFA did not report any Grade 3 or 4 toxicity. No patient suffered from severe liver decompensation.

3.3. Best Tumor Response. Of 55 patients, 8 (15%) showed complete remission, 21 (38%) partial remission, 8 (15%) stable disease, and 18 (33%) progressive disease. The best response for each type of therapy is shown along with the treatments in Table 2.

3.4. Follow-Up and Overall Survival. Median follow-up time was 11.7 months (range 0.9–51.1). Forty-three of the 55 (78.2%) patients died during the follow-up period. The median number of follow-up visits was 3 (range: 1–15). The median overall survival period was 33.1 months (95% CI 16.5–49.8 months) from the time of first diagnosis and 16.0 months (95% CI 8.8–32.2 months) from the time of first local therapy at our institution (Figures 2(a) and 2(b)). A subgroup analysis by UICC stage showed a median survival of 15.9 months (95% CI 11.9–19.9 months) for patients with stage I disease, 9

Table 3: Cox regression analysis of the prognostic factors of the patient survival period.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
Age (≤65 years versus >65 years)	0.83	0.45–1.53	0.551			
Sex (male versus female)	1.17	0.64–2.12	0.615			
Previous resection (no versus yes)	0.73	0.37–1.43	0.358			
UICC at first therapy (stage I versus stages II–IV)	1.20	0.96–1.50	0.133			
Lobar spread of disease (unilobar versus bilobar)	1.47	0.78–2.76	0.237			
Extrahepatic metastasis (no versus yes)	1.55	0.78–3.09	0.211			
Tumor load (≤10% versus >10%)	1.81	0.99–3.31	0.055			
Number of lesions (1 versus >1)	2.44	1.27–4.71	**0.008**	2.85	1.43–5.65	**0.003**
Portal vein thrombosis (no versus yes)	1.43	0.62–3.30	0.407			
Vascular infiltration (no versus yes)	1.20	0.65–2.24	0.560			
Ascites (no versus yes)	1.49	0.66–3.35	0.314			
Liver cirrhosis (no versus yes)	1.25	0.67–2.34	0.493			
Biliary obstruction (no versus yes)	1.02	0.53–1.97	0.950			
ECOG index (0 versus 1–4)	1.23	0.66–2.30	0.511			
CA19–9 (≤39.9 U/mL versus >39.9 U/mL)	1.93	1.01–3.68	**0.047**	2.05	0.99 – 4.22	**0.052**
CEA (≤3.4 ng/mL versus >3.4 ng/mL)	2.30	1.23–4.31	**0.009**	1.89	0.97 – 3.72	**0.025**
Objective response (CR + PR versus SD + PD)	2.43	1.28–4.60	**0.006**	2.84	1.41 – 5.72	**0.003**
Complications (no versus yes)	1.06	0.68–1.67	0.796			
Tumor size (≤50 mm versus >50 mm)	1.35	0.74–2.46	0.328			
Tumor size (≤100 mm versus >100 mm)	1.22	0.60–2.50	0.585			

HR, hazard ratio; CI, confidence interval; objective response categories, see Table 2.

months (95% CI 0.8–17.2 months) for patients with stage IIIa, 18.4 months (95% CI 8.1–28.7 months) for patients with stage IIIc, and 13 months (95% CI 6–18.9 months) for patients with stage IV. Only 5 patients were in stage II when they received first local therapy and, of these, 3 were still alive and therefore censored at the time of analysis. There was no significant difference in survival between the various stages.

3.5. Factors Related to Patients' Survival Period. The following variables were found to be significant in the univariate analysis (Table 3) and were entered into the multivariate Cox regression model: number of tumor lesions, the tumor markers carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9), and objective response. The multivariate analysis showed that these parameters were independent factors associated with duration of survival after therapy. According to the Kaplan-Meier analysis, factors identified as influencing median overall survival (after first local treatment) were number of tumors (1 versus ≥2), 34 versus 12.3 months, $p = 0.006$; elevated CA 19-9 levels (normal versus above normal), 23.2 versus 15.9 months, $p = 0.043$; elevated CEA levels (normal versus above normal),

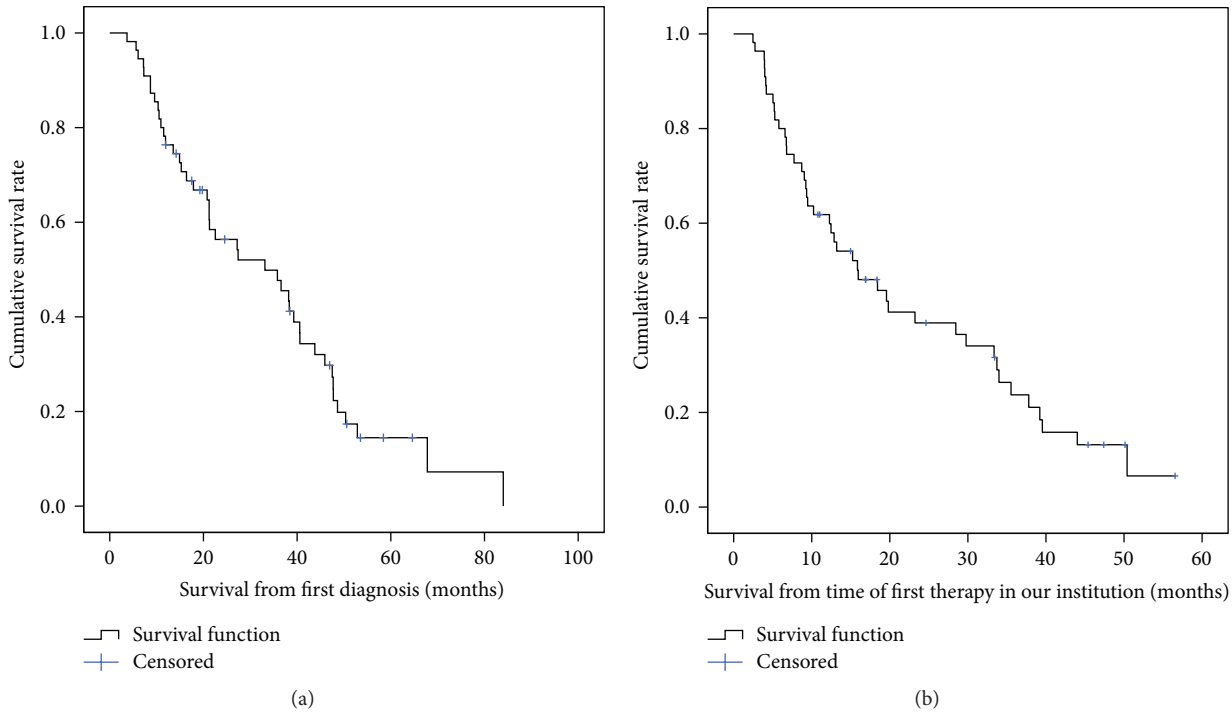

Figure 2: Overall survival rate in all patients from time of first diagnosis (a) and from time of first therapy at our institution (b). Median overall survival from time of first diagnosis: 33.1 months (95% CI 16.5–49.8 months). Median overall survival from time of first therapy at our institution: 16.0 months (95% CI 8.8–32.2 months).

29.8 versus 9.1 months, $p = 0.007$ (the upper normal limits were taken to be 39.9 U/mL for CA 19-9 and 3.4 ng/mL for CEA); and objective response according to RECIST, 29.8 versus 9.3 months, $p = 0.005$. Corresponding survival curves are shown in Figures 3(a)–3(d).

4. Discussion

ICC (intrahepatic cholangiocarcinoma of the mass-forming type) is a uniformly fatal disease with a poor prognosis when detected at an advanced stage. Unfortunately most patients present with unresectable disease because of the absence of symptoms until late in disease progression. Published data concerning systemic or local therapy options are limited. Furthermore, most studies fail to provide a clear profile of their patients in respect of tumor stage or metastatic disease and often comprise heterogeneous study populations including patients with Klatskin tumors, ampullary carcinoma, and gallbladder carcinoma. Therefore, direct comparison with systemic or standard locoregional therapy approaches is sometimes difficult.

We sought to investigate the outcome of a patient-tailored therapy course, including all modalities of minimally invasive oncology, applied alone or in combination, singly or repeatedly, following an interdisciplinary treatment algorithm for patients with mass-forming ICC only. In our study the clinical stage of patients was well described, and tumor disease was staged according to the UICC tumor node metastasis (TNM) classification system.

Our study showed a median survival of 16 months from first local therapy and 33.1 months from first diagnosis, which is higher than that found in most of the earlier studies examining different locoregional therapies. Kiefer et al. [12] reported a median survival of 15 months from chemoembolization and 20 months from diagnosis. In their study 62 patients with heterogeneous tumor entities were treated, 37 with histologically proven ICC and 25 with poorly differentiated adenocarcinoma of unknown primary origin; 49% of the patients presented with UICC (TNM) stage IIIa and 24% with stage IV, comparable to our study where 40% of patients presented with stage IIIc and 25% with stage IV. Survival data concerning different UICC stages are unfortunately not reported.

In a study conducted by Park et al. 72 patients (61% stage IIIa/IIIb and 19% stage IV) with untreated, unresectable ICC received TACE as first-line therapy. Survival after diagnosis was measured and compared with that of patients who received supportive therapy only [10]. Median survival was shorter than in our study: 12.2 months for the TACE group and 3.3 months for the "supportive treatment" group.

Another study assessing survival after RE was published by an Australian group in 2010. In that study, 25 patients underwent RE in advanced ICC: 60% had >25% tumor burden, 48% showed extrahepatic metastasis, and 76% had previous antitumor treatments. Seven patients (26%) underwent ivCTX after RE. The median survival after diagnosis of ICC was 20.4 months and after RE 9.3 months, but for 13

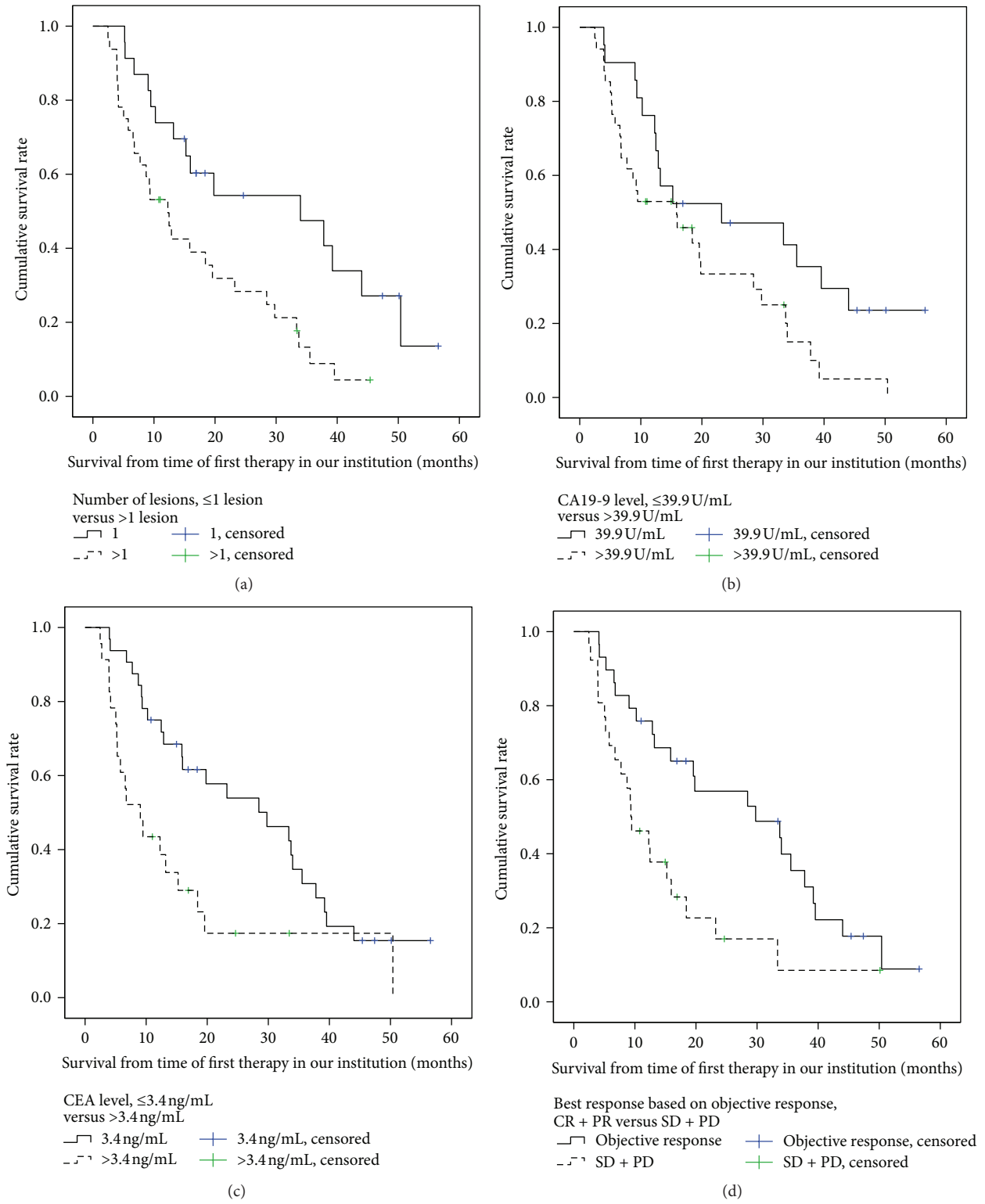

Figure 3: Overall survival rate in all patients according to influencing factors (derived from Cox model, Table 3). (a) Overall survival rates with regard to number of lesions (≤1 lesion versus >1 lesion), with a median overall survival of 34 and 12.3 months, $p = 0.006$. (b) Overall survival rates with regard to CA 19-9 level (≤39.9 U/mL versus >39.9 U/mL) with a median overall survival of 23.2 and 15.9 months, $p = 0.043$. (c) Overall survival rates with regard to CEA level (≤3.4 ng/mL versus >3.4 ng/mL), with a median overall survival of 29.8 and 9.1 months, $p = 0.007$. (d) Overall survival rates with regard to best response (objective response (CR and PR) versus stable and progressive disease (SD + PD)), with a median overall survival of 29.8 and 9.3 months, $p = 0.005$.

patients with hepatic disease only a median survival of 16.3 months was achieved [8].

Excellent results have been reported for 13 patients with 17 unresectable but small ICC (10 tumors < 3 cm, 5 tumors 3–5 cm, and 2 tumors > 5 cm) treated by RFA in an early tumor stage (8 stage I, 3 stage II, 1 stage IIIb, and 1 stage IV). They presented a median overall survival period of 38.5 months [11].

Schnapauff et al. evaluated outcomes after repeated interstitial HDR-BT (27 sessions) in 15 patients with unresectable ICC who did not show extrahepatic metastasis and suffered from limited hepatic disease only (<5 lesions), revealing a median survival of 11 months and 21 months after primary diagnosis [9].

Recently, results of a larger-scale randomized phase III trial of systemic therapy were published, comparing "gemcitabine alone" with "gemcitabine plus cisplatin" in a heterogeneous group of 410 patients with locally advanced or metastatic cholangiocarcinoma, gall-bladder cancer, or ampullary cancer. In that study the gemcitabine-cisplatin combination resulted in a significantly prolonged median overall survival of 11.7 months, compared with 8.1 months in the gemcitabine monotherapy group [7].

In summary, comparing our results with those from other studies on local-ablative therapies on ICC, we can conclude a comparatively long overall survival of our patient cohort, even though the stage of disease was mostly advanced according to UICC. Overall survival in our study cohort was substantially longer than in recent ivCTX-only studies [7]. However, since a significant proportion of our patients were already heavily pretreated with various treatments (including ivCTX) when receiving a first locoregional treatment of the liver, a selection bias towards a favorable tumor biology cannot be ruled out. However, irrespective of this potential bias, we were able to show an overall survival from first diagnosis that was comparable to that after surgical resection with curative intent (median survival of 27–36 months) [32–34].

In the present study 65% (36/55) of the patients had extrahepatic metastases (Table 1) before first treatment at our institution. In agreement with Gusani et al. [35] who reported the treatment outcome of ICC after TACE, we found that median survival after therapy did not differ significantly between patients with liver-only disease and patients suffering from extrahepatic metastasis as well. Similar findings have emerged from other studies on TACE and radioembolization of ICC [8, 12]. Additionally, overall survival was not affected by the UICC stage at the time of treatment at our institution. Regarding tumor characteristics, only the number of ICC lesions had an influence on survival (1 versus >1 lesion, $p = 0.006$). We claim that all these results indicate a pivotal change in the management and treatment of patients with advanced ICC disease. The importance of local tumor control as the main palliative goal has to be emphasized, regardless of extrahepatic metastases and stage of disease. This assumption is underlined by the finding that objective tumor response (liver only) was one of the independent factors influencing survival, with 29.8 months for OR and 9.3 months for SD/PD ($p = 0.005$). Obviously, prevention of liver failure due to progression of intrahepatic tumor (a frequent cause of mortality) is of utmost importance. According to our and others' results, effective suppression of liver tumors may prolong the survival period even in patients with advanced local disease and extrahepatic metastasis. We strongly believe that these findings should further promote clinical trials of local or locoregional therapies and that these may become a key modality in the treatment of nonresectable ICC in future.

Besides objective response and the number of ICC manifestations, only elevation of serum tumor markers CA 19-9 and CEA beyond normal levels showed a negative influence on survival. This might represent a more active tumor biology in patients with elevated tumor markers. Other factors included in our analysis (patient age and gender, prior liver-directed therapies, tumor size and stage, unilobar or bilobar tumor spread, portal vein thrombosis, vascular invasion, biliary obstruction, ascites, cirrhosis, therapy-related complications, ECOG status, Karnofsky index, and time from primary diagnosis to first local therapy) did not appear to affect outcome.

5. Conclusion

Our results show that patients with unresectable ICC of the mass-forming type may benefit from hepatic tumor control by local or locoregional therapies even with presence of extrahepatic spread. If local or locoregional therapies were deemed favorable by clinical means, therapeutic recommendations for a specific technique were driven by technical strengths or limitations of a given modality. As such, future prospective study formats should focus on supplementing systemic therapy by classes of interventions ("toolbox") rather than specific techniques, that is, local ablation leading to complete tumor destruction (such as RFA) or locoregional treatment leading to partial remission (such as radioembolization or TACE).

Abbreviations

ICC:	Intrahepatic cholangiocellular carcinoma
CTCAE:	National Cancer Institute Common Toxicity Criteria
95% CI:	95% confidence interval
CEA:	Carcinoembryonic antigen
CA 19-9:	Carbohydrate antigen 19-9
RECIST:	Response evaluation criteria in solid tumors
i.v.:	Intravenous
IvCTX:	Intravenous chemotherapy
RFA:	Radiofrequency ablation
RE:	^{90}Y-radioembolization
HDR-BT:	High dose rate brachytherapy
IaCTX:	Intra-arterial chemotherapy
TACE:	Transarterial chemoembolization
UICC:	Union for International Cancer Control
ECOG:	Eastern Cooperative Oncology Group
MRI:	Magnetic-resonance imaging
CT:	Computerized tomography
PVT:	Portal vein thrombosis

5-FU/FA: 5-Fluorouracil/leucovorin
TNM: Tumor node metastasis.

Conflict of Interests

All authors disclose that there is not any actual or potential conflict of interests related to the publication of this paper. Jens Ricke receives consulting fees, advisory arrangements, and research grants from SIRTEX Medical Limited and BAYER Healthcare. Maciej Pech receives consulting fees, speakers' bureau, research, and travel grants from SIRTEX Medical Limited. Ricarda Seidensticker, Max Seidensticker, and Holger Amthauer receive research and travel grants from SIRTEX Medical Limited.

Authors' Contribution

Ricarda Seidensticker and Max Seidensticker contributed equally to this work.

References

[1] B. Blechacz and G. J. Gores, "Cholangiocarcinoma: advances in pathogenesis, diagnosis, and treatment," *Hepatology*, vol. 48, no. 1, pp. 308–321, 2008.

[2] J. Yamamoto, T. Kosuge, T. Takayama et al., "Surgical treatment of intrahepatic cholangiocarcinoma: four patients surviving more than five years," *Surgery*, vol. 111, no. 6, pp. 617–622, 1992.

[3] M. J. Lieser, M. K. Barry, C. Rowland, D. M. Ilstrup, and D. M. Nagorney, "Surgical management of intrahepatic cholangiocarcinoma: a 31-year experience," *Journal of Hepato-Biliary-Pancreatic Surgery*, vol. 51, no. 1, pp. 41–47, 1998.

[4] K. M. Chu, E. C. Lai, S. Al-Hadeedi et al., "Intrahepatic cholangiocarcinoma," *World Journal of Surgery*, vol. 213, pp. 301–306, 1997.

[5] S. A. Khan, H. C. Thomas, B. R. Davidson, and S. D. Taylor-Robinson, "Cholangiocarcinoma," *The Lancet*, vol. 366, no. 9493, pp. 1303–1314, 2005.

[6] S. C. Cunningham, M. A. Choti, E. C. Bellavance, and T. M. Pawlik, "Palliation of hepatic tumors," *Surgical Oncology*, vol. 16, no. 4, pp. 277–291, 2007.

[7] J. Valle, H. Wasan, D. H. Palmer et al., "Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer," *The New England Journal of Medicine*, vol. 362, no. 14, pp. 1273–1281, 2010.

[8] A. Saxena, L. Bester, T. C. Chua, F. C. Chu, and D. L. Morris, "Yttrium-90 radiotherapy for unresectable intrahepatic cholangiocarcinoma: a preliminary assessment of this novel treatment option," *Annals of Surgical Oncology*, vol. 17, no. 2, pp. 484–491, 2010.

[9] D. Schnapauff, T. Denecke, C. Grieser et al., "Computed tomography-guided interstitial HDR brachytherapy (CT-HDRBT) of the liver in patients with irresectable intrahepatic cholangiocarcinoma," *CardioVascular and Interventional Radiology*, vol. 35, no. 3, pp. 581–587, 2012.

[10] S.-Y. Park, J. H. Kim, H.-J. Yoon, I.-S. Lee, H.-K. Yoon, and K.-P. Kim, "Transarterial chemoembolization versus supportive therapy in the palliative treatment of unresectable intrahepatic cholangiocarcinoma," *Clinical Radiology*, vol. 66, no. 4, pp. 322–328, 2011.

[11] J. H. Kim, H. J. Won, Y. M. Shin, K.-A. Kim, and P. N. Kim, "Radiofrequency ablation for the treatment of primary intrahepatic cholangiocarcinoma," *American Journal of Roentgenology*, vol. 196, no. 2, pp. W205–W209, 2011.

[12] M. V. Kiefer, M. Albert, M. McNally et al., "Chemoembolization of intrahepatic cholangiocarcinoma with cisplatinum, doxorubicin, mitomycin C, ethiodol, and polyvinyl alcohol," *Cancer*, vol. 117, no. 7, pp. 1498–1505, 2011.

[13] L. Sobin, M. K. Gospodarowicz, and C. Wittekind, *TNM Classification of Malignant Tumours*, Wiley-Liss, New York, NY, USA, 6th edition, 2002.

[14] Y. C. Yoon, K. S. Lee, Y. M. Shim, B.-T. Kim, K. Kim, and T. S. Kim, "Metastasis to regional lymph nodes in patients with esophageal squamous cell carcinoma: CT versus FDG PET for presurgical detection prospective study," *Radiology*, vol. 227, no. 3, pp. 764–770, 2003.

[15] S.-Y. Park, J. H. Kim, H. J. Won, Y. M. Shin, and P. N. Kim, "Radiofrequency ablation of hepatic metastases after curative resection of extrahepatic cholangiocarcinoma," *American Journal of Roentgenology*, vol. 197, no. 6, pp. W1129–W1134, 2011.

[16] G. Carrafiello, D. Laganà, E. Cotta et al., "Radiofrequency ablation of intrahepatic cholangiocarcinoma: preliminary experience," *CardioVascular and Interventional Radiology*, vol. 33, no. 4, pp. 835–839, 2010.

[17] J. Ricke, P. Wust, A. Stohlmann et al., "CT-guided interstitial brachytherapy of liver malignancies alone or in combination with thermal ablation: phase I-II results of a novel technique," *International Journal of Radiation Oncology Biology Physics*, vol. 58, no. 5, pp. 1496–1505, 2004.

[18] R. Rühl and J. Ricke, "Image-guided micro-therapy for tumor ablation: from thermal coagulation to advanced irradiation techniques," *Onkologie*, vol. 29, no. 5, pp. 219–224, 2006.

[19] A. H. Mahnken, P. Bruners, and R. W. Günther, "Techniques of interventional tumor therapy," *Deutsches Arzteblatt*, vol. 105, no. 38, pp. 646–653, 2008.

[20] G. Wieners, M. Pech, B. Hildebrandt et al., "Phase II feasibility study on the combination of two different regional treatment approaches in patients with colorectal 'liver-only' metastases: hepatic interstitial brachytherapy plus regional chemotherapy," *CardioVascular and Interventional Radiology*, vol. 32, no. 5, pp. 937–945, 2009.

[21] R.-T. Hoffmann, P. M. Paprottka, A. Schön et al., "Transarterial hepatic yttrium-90 radioembolization in patients with unresectable intrahepatic cholangiocarcinoma: factors associated with prolonged survival," *CardioVascular and Interventional Radiology*, vol. 35, no. 1, pp. 105–116, 2012.

[22] R. Seidensticker, T. Denecke, P. Kraus et al., "Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases," *CardioVascular and Interventional Radiology*, vol. 35, no. 5, pp. 1066–1073, 2012.

[23] O. N. Kucuk, C. Soydal, S. Lacin, E. Ozkan, and S. Bilgic, "Selective intraarterial radionuclide therapy with Yttrium-90 (Y-90) microspheres for unresectable primary and metastatic liver tumors," *World Journal of Surgical Oncology*, vol. 9, article 86, 2011.

[24] J. H. Kim, H.-K. Yoon, K.-B. Sung et al., "Transcatheter arterial chemoembolization or chemoinfusion for unresectable intrahepatic cholangiocarcinoma: clinical efficacy and factors influencing outcomes," *Cancer*, vol. 113, no. 7, pp. 1614–1622, 2008.

[25] T. J. Vogl, S. Zangos, K. Eichler et al., "Radiological diagnosis and intervention of cholangiocarcinomas (CC)," *Fortschr Röntgenstr*, vol. 184, no. 10, pp. 883–892, 2012.

[26] J. Ricke, B. Hildebrandt, A. Miersch et al., "Hepatic arterial port systems for treatment of liver metastases: factors affecting patency and adverse events," *Journal of Vascular and Interventional Radiology*, vol. 15, no. 8, pp. 825–833, 2004.

[27] M. Cantore, A. Mambrini, G. Fiorentini et al., "Phase II study of hepatic intraarterial epirubicin and cisplatin, with systemic 5-fluorouracil in patients with unresectable biliary tract tumors," *Cancer*, vol. 103, no. 7, pp. 1402–1407, 2005.

[28] T. J. Vogl, S. Zangos, K. Eichler, J. B. Selby, and R. W. Bauer, "Palliative hepatic intraarterial chemotherapy (HIC) using a novel combination of gemcitabine and mitomycin C: results in hepatic metastases," *European Radiology*, vol. 18, no. 3, pp. 468–476, 2008.

[29] J. R. A. Skipworth, S. W. M. Olde Damink, C. Imber, J. Bridgewater, S. P. Pereira, and M. Malagó, "Review article: surgical, neo-adjuvant and adjuvant management strategies in biliary tract cancer," *Alimentary Pharmacology and Therapeutics*, vol. 34, no. 9, pp. 1063–1078, 2011.

[30] M. Fuchs and W. Schepp, "Is there a nonsurgical therapeutic approach to cholangiocellular carcinomas?" *Chirurg*, vol. 77, no. 4, pp. 341–351, 2006.

[31] E. A. Eisenhauer, P. Therasse, J. Bogaerts et al., "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)," *European Journal of Cancer*, vol. 45, no. 2, pp. 228–247, 2009.

[32] I. Endo, M. Gonen, A. C. Yopp et al., "Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection," *Annals of Surgery*, vol. 248, no. 1, pp. 84–96, 2008.

[33] S. Yedibela, R. Demir, W. Zhang, T. Meyer, W. Hohenberger, and F. Schönleben, "Surgical treatment of mass-forming intrahepatic cholangiocarcinoma: an 11-year western single-center experience in 107 patients," *Annals of Surgical Oncology*, vol. 16, no. 2, pp. 404–412, 2009.

[34] R. Dhanasekaran, A. W. Hemming, I. Zendejas et al., "Treatment outcomes and prognostic factors of intrahepatic cholangiocarcinoma," *Oncology Reports*, vol. 29, no. 4, pp. 1259–1267, 2013.

[35] N. J. Gusani, F. K. Balaa, J. L. Steel et al., "Treatment of unresectable cholangiocarcinoma with gemcitabine-based transcatheter arterial chemoembolization (TACE): a single-institution experience," *Journal of Gastrointestinal Surgery*, vol. 12, no. 1, pp. 129–137, 2008.