ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Research Article

Diagnosis and Treatment of Obstructive Jaundice Syndrome

Fomicheva Natalya[1]*, Shuleshova A[2], Ulyanov D[1], Danilov D[2] and Vasilenko O[3]

[1]*Central Clinical Hospital with a Polyclinic of the Administrative Department of the President of the Russian Federation, Russia*

[2]*National Medical Research Center of Cardiology of the Ministry of Health of Russia, Russia*

[3]*United Hospital with a Polyclinic of the Administrative Department of the President of the Russian Federation, Russia*

***Corresponding Author:** Fomicheva Natalya, Endoscopic Department, Moscow Central Clinical Hospital with Polyclinic Administration of the President of the Russian Federation, Moscow, Russia.

Received: August 22, 2020; **Published:** September 15, 2020

Abstract

The literature data on the efficacy of various methods of diagnosis of obstructive jaundice syndrome caused by stones and bile duct strictures of various origins were analyzed. The analysis of own data was made on the efficacy and accuracy of cholangioscopy and confocal laser endomicroscopy to diagnose the causes of biliary obstruction. The efficacy of endoscopic retrograde cholangiopancreatography was considered in combination with additional examination methods.

Keywords: *Cholangiocarcinoma; Cholangioscopy; Confocal Laser Endomicroscopy; Obstructive Jaundice; Bile Duct Stones; Pancreatic Cancer*

Abbreviations

CLE: Confocal Laser Endomicroscopy; ERCP: Endoscopic Retrograde Cholangiopancreatography; MRCP: Magnetic Resonance Cholangiopancreatography; CT: Computer Tomography; EUS: Endoscopic Ultrasonography; CS: Cholangioscopy; BT: Biliary Tract; PET: The Positron Emission Tomography

Introduction

The problem of diagnosing the causes of obstructive jaundice and its treatment is still one of the most pressing and complex challenges for the urgent abdominal surgery. Ascending infection leading to multiple organ failure necessitates prompt identification of the etiological factor, develop adequate therapeutic approach and eliminate the cause. The complication rate, which remains high despite all current medical achievements. Moreover, postoperative mortality among the elderly and old can reach 15 - 25% [1].

In the etiology of obstructive jaundice two main groups can be distinguished 1) bile duct stones, 2) strictures.

Benign etiology of strictures includes inflammation (in particular, accompanying primary sclerosing cholangitis), acute pancreatitis with bile duct compression by the edematous head, chronic pancreatic pseudotumor, iatrogenic (injury, coagulation trauma or common bile duct ligation), and parasitic invasion.

Malignant processes leading to biliary strictures include pancreatic head tumors, cholangiocarcinoma, gallbladder cancer, and metastasis to the portal fissure. Some extremely rare conditions like gallbladder lymphoma and metastasis to the bile duct wall [2] should also be kept in mind, as they can also result in obstructive jaundice.

Increasing number of patients may present with extrahepatic bile ducts strictures of various origin against the background of increasing incidence of malignancies in the pancreatobiliary area which accounts for about 15% of all digestive tract malignant tumors [3]. Accurate differential diagnosis of biliary strictures is of key importance for the correct choice of surgical approach.

Despite the improvements in the endoscopic techniques: narrow band imaging digital cholangioscopy (NBI), confocal laser endomicroscopy (CLE) and new developments in the field of genetic research (fluorescence in situ hybridization, FISH), differentiating benign from malignant biliary strictures still remains a difficult task [4]. This is a vital issue for Russia where the malignant aetiology needs to be confirmed morphologically to justify surgical intervention. Morphological verification is also important for the adequate chemotherapy selection. It should be noted that the diagnosis of cholangiocarcinoma is the most difficult task due to peculiarities of its growth as the tumor often spreads along and inside the duct wall.

Materials and Methods

The study included the results of examination and treatment of 213 obstructive jaundice patients that received treatment at the Central Clinical Hospital with Polyclinic of the Administrative Department of the President of the Russian Federation in 2010 - 2015. The patients were recruited consecutively, without any selection or exclusion.

All patients underwent screening laboratory tests, transabdominal ultrasound of the abdominal cavity, esophagogastroduodenoscopy with examination of the major duodenal papilla area. Magnetic resonance cholangiopancreatography (MRCP) or computer tomography (CT) were used as qualifying diagnostic methods. The MRCP was performed for suspected bile duct stones.

CT scan was performed if a tumor lesion was suspected in order to clarify operability. Endoscopic ultrasonography (EUS) was performed when the MRCP findings were not clear or when MRCP could not be done. All patients underwent minimally invasive bile ducts interventions to decompress the biliary system and/or visually assess the condition of the extrahepatic bile ducts. The patients were divided into two groups: (1) the main group consisted of 105 people who, besides endoscopic retrograde cholangiopancreatography (ERCP), underwent cholangioscopy (CS) which in 22 cases was supplemented with intraductal confocal laser endomicroscopy (CLE); (2) the control group included 108 patients who underwent only ERCP and/or transpapillary surgery.

The groups were comparable by gender and age. The study included patients of both genders aged 24 to 86. The male/female ratio in the main group was 50%/50%. There were more women in the control group (58%). The average age of patients was 66 ± 13.3 years and 64 ± 14.4 years, respectively.

The distribution of patients by the etiology of obstructive jaundice is shown in figure 1.

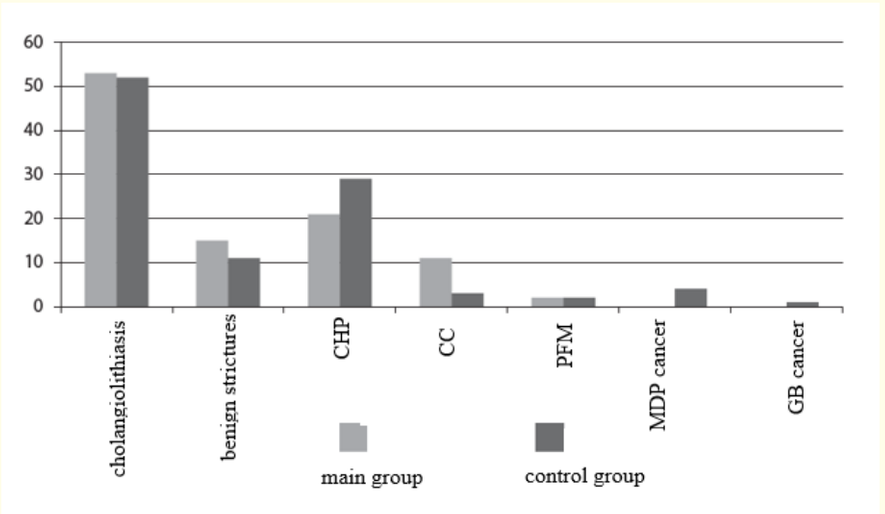

Figure 1: *The distribution of patients by the etiology of obstructive jaundice. CHP: Cancer of the Head of the Pancreas; CC: Cholangiocarcinoma; PFM: Portal Fissure Metastases; MDP Cancer: Major Duodenal Papilla Cancer; GB: Cancer, Gall Bladder Cancer.*

Figure 1 shows that, according to our data, choledocholithiasis and cancer of the head of the pancreas (CHP) are the main causes in the genesis of obstructive jaundice.

In both benign and malignant diseases accompanied by biliary obstruction and manifested by the cholestasis syndrome, after preliminary diagnosis and a short period of preoperative preparation, the patients underwent ERCP with therapeutic transpapillary interventions aimed at adequate bile ducts decompression. By standard indications, after access to the bile ducts and endoscopic papillotomy, mechanical stone extraction, mechanical lithotripsy, and endoscopic stenting were performed.

When a stricture was detected, the material was taken for cytological and histological verification. The biopsy was made with special bile duct forceps with the possibility of FB-39Q-1 (Olympus) contrast. The biopsy material was considered appropriate after obtaining at least 2 fragments visually sufficient for morphological examination. Biopsy sampling of cytological material from the stricture area was done with disposable CytoMax II (Cook) brushes introduced into bile ducts through the preinstalled guide wire.

The intraoperative manipulations were made with the FCN-15X (Pentax) operating cholangioscope (4.9 mm insert diameter), transpapillary CS - with the CHF-B 20 (Olympus) baby scope inserted through the wide-channel TJF-M20 (Olympus) duodenoscope. The thin transnasal gastroscope GIF-N 180 (Olympus) (4.9 mm insert diameter) was also used to examine the bile ducts.

The indications for diagnostic cholangioscopy were as follows: (1) the impossibility of reliable X-ray visualization of small stones or fragments of large stones (after lithotripsy due to their contrast staining or aerobilia simulating stones after adequate papillotomy), (2) assessment of the condition of the mucous membrane of the biliary tract (BT) when cholangitis is suspected, (3) clarification of the BT architecture and the state of the BT lumen (in the differential diagnosis of the cause of extrahepatic BT stenosis in the absence of filling of one of the lobular ducts, if the presence of a foreign body is suspected, at irregular BT contour on cholangiogram), (4) targeted biopsy and brush cytology from the area of the strictures and neoplasms, (5) confocal laser endomicroscopy.

The reasons for using therapeutic cholangioscopy were: (1) visually controlled mechanical extraction of "difficult" and "uncomfortable" stones (small stones from lobular ducts, from the cystic duct remnant), (2) passing the guide string through the BT strictures under visual control, (3) targeted capture and removal of foreign bodies (migrated stents, bile duct drain fragments), (4) visually controlled sanitation of the bile ducts (to assess sanitation adequacy), (5) electrohydraulic lithotripsy of large stones.

Cholangioscopy was performed in two patterns: (1) intraoperatively, during surgery of the organs of the pancreatic biliary area with the device passing through an incision of the common bile duct (7 manipulations); (2) at ERCP, transpapillary after EPT (98 manipulations in total; with a baby scope in 32 patients, a transnasal gastroscope in 66 patients).

For intraductal CLE, the Cellvizio (Mauna Kea Technologies) system and special bile duct probes were used. The systemic contrast was 1.0 ml of 10% sodium fluorescein solution intravenously through a peripheral catheter.

The indication for CLE was a suspected malignant genesis of the stricture, including suspected invasion of a pancreatic tumor into the bile duct wall. During cholangioscopy, the confocal microscope probe was moved to the stricture area either independently or through the ultrathin endoscope channel.

Results

ERCP was managed in all patients of the main group and in 107 (99%) of 108 patients in the control group.

Decompression stenting proved effective in 47 (100%) of 47 patients in the main group, and in 48 (97%) of 49 patients in the control group. ERCP and biliary decompression failed in one patient due to the MDP orifice location in a technically inconvenient area at the large diverticulum bottom. The percutaneous transhepatic cholangiostomy was performed in this patient.

49 plastic and 22 metal stents were installed in 71 patients with malignant strictures.

At the second stage of the endoscopic therapy, 23 plastic stents were replaced with metal ones due to the patients' inoperability. Such complications considered associated with stenting as acute pancreatitis (due to the Wirsung's duct exit obstruction by a dilated stent), perforation of the bile duct or duodenum wall (caused by the injury during the stent placement) or decubitus ulcer of the duodenum wall (due to stent migration) were not observed in the analyzed groups. There was a single case of acute cholecystitis in a 67-year-old man on the next day after ES; most likely, it was associated with the cystic duct orifice occlusion by an opened stent. The inflammation was arrested conservatively with appointment of intravenous antibiotic injections; the patient then, in 4 days, underwent laparoscopic cholecystectomy.

Besides ERCP, all patients of the main group underwent transpapillary cholangioscopy. In 4 cases, this type of intervention in cholelithiasis patients made it possible to reveal the stone remains that were not visualized radiographically, and in 4 cases to exclude their presence, despite obvious filling corporals in X-ray images.

In 6 cases, CS was performed transpapillary as an independent manipulation during routine duodenoscopy (without X-ray imaging) and in one of these cases with lithoextraction. CS failed in 6 (5.6%) of 107 patients. Failures in all 6 cases were observed during oral cholangioscopy with a transnasal device and explained by the difficulty of introducing the endoscope into the newly formed orifice of the common bile duct swollen after EPT. Therapeutic CS was also unsuccessful in one case as the stone could not be removed from the cystic duct stump. No complications were noticed during CS as such.

Based on our studies, the following typical signs of benign and malignant strictures have been identified: Changes in the duct mucosa at benign stricture: (1) The narrowing of the duct lumen is predominantly circular; (2) The mucous membrane is of pale shade and easily injured; (3) The vascular pattern is blurred; (4) On the mucous membrane and in the lumen, fibrin plaque in the form of threads is noted. With severe cholangitis, the mucous membrane has a whitish, velvety appearance; (5) The elasticity of the stricture. The passage of the narrowing area with a cholangioscope is possible in some cases with a slight dilation.

Typical signs of malignant strictures: (1) Lumen asymmetry. The lumen is often of a crescent shape. In some cases, the mucosa looks "bumpy" on one of the CBD walls; (2) Mucous membrane ulceration; (3) Mucous membrane changes color from bright hyperemia to brown; (4) Vascular pattern violation (however, visualized only when the device is used at NBI mode); (5) "Hard" stricture. Cholangioscope passage is impossible.

Cholangioscopy allowed selective localization of the lesion and collection of specimen from the targeted area, so it was feasible to verify the diagnosis and exclude the malignant etiology of the stricture in 3 out of 26 patients, and to confirm the malignant aetiology in 5 cases. In these 26 patients, the aetiology of the stricture remained unclear at the time of ERCP, despite the entire complex of diagnostic non-invasive studies.

CLE was performed in 22 of 26 patients in whom ERCP could not detect the aetiology of the stricture.

The results of the combined use of CLE, CS and morphological studies are shown in table 1.

		Sensitivity	Specificity	Accuracy
	n	(%)	(%)	(%)
CS	26	80	58	70
CS + CLE	22	84	66	81
CS + CLE + biopsy and cytology	22	94	75	90

Table 1: *Results of diagnostic techniques used to clarify the stricture etiology. CS: Cholangioscopy; CLE: Confocal Laser Endomicroscopy.*

According to the data obtained (Table 1), cholangioscopy is featured with relatively high sensitivity (80%), while its specificity is low and (58%). At the same time, the combination of cholangioscopy and CLE increased not only the sensitivity (84%) but also the specificity (66%) of diagnosis. We believe that the cause of false positive results is overdiagnosis associated with the lack of experience at the stage of mastering the technique. Supplementing visual techniques with morphological studies can increase the diagnostic sensitivity up to 94% with an accuracy of 90%.

In the postoperative period, one complication was recorded in one patient (0.9%) out of 108 patients in the control group. A 58-year-old woman after ERCP with the CBD revision was complicated postoperatively with pancreatic necrosis that required surgical intervention with the patient staying in the ICU for 6 days. With the conducted therapy, she has recovered. Transient amylasemia was observed in 36 patients in the main group and in 39 patients in the control group, accompanied by abdominal pain in 11 and 17 patients, respectively. In all cases, the pain syndrome did not require narcotic analgesia. The amylasemia rate in all cases was decreasing during 3 - 4-day therapy and did not require intensive therapy and/or ICU stay. There were no lethal cases.

Discussion

Screening laboratory diagnostics with defining specific tumor markers and routine transabdominal ultrasound of the abdominal organs still are the measures of the first stage in diagnosing the causes of obstructive jaundice. They allow suspecting the cause and determining further examination tactics. Choosing the second step is more complicated.

According to a prospective study [5], the MRCP sensitivity and specificity in the cholangiolithiasis diagnosis exceeds 90% and there is no risk of complications that are observed after ERCP. The EUS efficacy in diagnosing cholangiolithiasis, according to several authors, reaches 100%. However, according to our data, in the presence of inflammation and/or biliary “sludge” in the ducts, the EUS and MRCP specificity in diagnosing cholangiolithiasis, may decrease.

In addition, not a single diagnostic technique allows performing the lithoextraction as such. Intraoperative cholangiography is associated with longer operation and exposure of the patient and staff to radiation, while the high sensitivity of the method is questionable: according to a large study, performing cholangioscopy after radiologically “adequate” sanitation in 29% of cases revealed missed stones [6]. After stone removal, follow-up cholangiography is usually not performed; therefore, the likelihood of leaving small stones or fragments increases, and as was shown in two large studies, fragmentation of stones during extraction leads to cholangiolithiasis recurrence [7]. Intraoperative ultrasound was found to be effective only for detecting intrahepatic stones.

Despite current progress in imaging methods, cholangiocarcinoma diagnosing is especially difficult due to the features of its growth. In cholangiocarcinoma, the tumor mass itself is usually absent in the early stages, and traditional screening diagnostic methods, ultrasound, CT and MRI are not only limited in sensitivity but also have unsatisfactorily low specificity [8]. According to a study in India in 429

patients with obstructive jaundice, ultrasound revealed obstruction of the duct in 89% of cases with a sensitivity of localization of the obstruction level of 94% [9]. According to E.I. Galperin's data, the information content of ultrasound on the block level does not exceed 78% [3]. It should be noted that in some cases the changes in cholangiocarcinoma do not differ from those in metastatic lesions [10]. CT happens to be informative only in the presence of tumor masses in the duct lumen and of distant metastases. According to T Rösch., *et al*. the sensitivity and specificity of CT in diagnosing malignant strictures is 77% and 63%, respectively [11]. With CT, the likelihood of false-negative results for tumors of the head of the pancreas less than 3 cm in size increases significantly when they block the main pancreatic duct [12]. The MRCP allows imaging the bile ducts as good as ERCP, however, the "static" images are a disadvantage of the method. Besides, MRCP has low accuracy in determining the degree of strictures and does not provide complete information on the spread of the tumor process relative to hepaticocholedochus (with invasive growth), and the extent of fibrous changes in benign corrosive strictures, thus complicating the choice of surgical approach [13]. The positron emission tomography (PET) is capable of determining the localization of the primary process, as well as the presence and prevalence of metastases. However, according to Russian researchers, PET cannot visualize small tumors, and its use is inappropriate if it is necessary to differentiate malignant diseases from inflammatory changes, including in the tissues surrounding the tumor [14]. CD Anderson., *et al*. also reported limitations in the use of PET associated with false positive results in the presence of biliary tract infection, in primary sclerosing cholangitis, as well as after interventions on the bile ducts at ERCP and PCS [15]. According to MJ Reinhard., *et al*. PET does not increase the accuracy in non-invasive diagnosis of intra- and extrahepatic cholangiocarcinoma and bile duct strictures, which, according to the authors, may be due to the small size of the tumor [16]. Given the dubious diagnostic value and, at the same time, the high cost of the study, PET is currently not widely used in Russia.

The ERCP remains the main diagnostics method and minimally invasive treatment of diseases of the extrahepatic bile ducts, since it is the only research method that can be instantaneously supplemented with a whole range of transpapillary diagnostic and therapeutic procedures. In addition, intraluminal drain is the most functional treatment for obstructive jaundice. Currently, the efficacy of this area of surgery can be increased by introducing additional visual diagnostic methods, CS and CLE.

The use of direct visualization of the bile ducts allows obtaining additional information both from the CBD lumen and directly from the stricture area [8]. The fiber-optic endoscopic devices earlier developed for this purpose are giving way to HD digital video cholangioscopes able to visualize with the narrow band interference (NBI) and have broader channel for manipulations, e.g. taking histological material. In a multicenter study (n = 144), T Itoi, H Maguchi., *et al*. showed that with good sensitivity (87%), the specificity of the "blind" biopsy in determining the nature of the stricture did not exceed 79% [17]. It was assumed that performing the visually controlled forceps biopsy will increase its information content. In a multicenter study, Japanese researchers reported that cholangioscopy supplemented with biopsy under visual control can increase the specificity of diagnosing the causes of stricture to 96% with an accuracy of up to 98% [17]. In another prospective study analyzing 53 cases, JJ Tischendorf., *et al*. also demonstrated the efficacy of biopsy under cholangioscope guidance; specificity was 93% with an accuracy of 93% [18].

Our data showed that the sensitivity of cholangioscopy-guided biopsy was 45% with a specificity of 100%. The low sensitivity of targeted biopsy in the present study was probably due to the small number of fragments taken for investigation.

Confocal laser endomicroscopy is a basically novel technique in the differential diagnostics of extrahepatic bile duct strictures. It is based on the principle of obtaining images with the software analysis of a laser beam reflected from cellular structures which "appear" against the background of the luminescence of a fluorescent substance introduced into a peripheral vein and circulating through the capillaries of the tissue under study. The technique makes it possible to recognize the malignant aetiology of strictures at the stage of the tumor microfocus, revealing a destruction of the vascular micropattern, dilated plethoric capillaries, and reflecting enhanced neoangiogenesis specific for malignant tumors. According to foreign authors, the CLE sensitivity is 83% and the specificity reaches 75% [19]. According to our data, based on a small number of our studies, the sensitivity of the method was 84% with a specificity of 66% (Table 1). However, we believe that the specificity of the studies of the kind can be increased through further gain in experience.

Conclusion

The issue of the appropriateness of diagnostic ERCP in the era of MRCP and EUS still remains debatable. Among the indisputable advantages of ERCP, there is the possibility of taking histological material and performing therapeutic manipulations. Also, in a prospective randomized study, the cost-effectiveness of ERCP, rather than MRCP, as the first stage of diagnostics was demonstrated with statistical significance.

The presence of a stricture in the bile ducts, regardless of whether its cause is known or not, is alarming. Differentiating benign from malignant strictures can be a difficult task not only for the clinician, but also for experts in imaging diagnostics, due to the peculiarities of the spread of cholangiocarcinoma in the bile ducts. Such conventional imaging methods as ultrasound, CT and MRCP have limited sensitivity in specifying the genesis of stricture, and in some cases the level of obstruction, and directly depend on the level of equipment and the experience of the specialist sitting at the control panel. The presence of a number of non-malignant conditions manifested by strictures in the bile ducts requires a multimodal approach to this problem.

Despite the use of various techniques, the information content of both biopsy and cytology from the stricture area remains low.

In this regard, a promising direction is genetic studies of the material taken that, as has already been shown in a number of studies, can significantly increase the informative value. What is especially valuable, the informative value (both sensitivity and specificity) of the already taken morphological material increases. However, these techniques have not yet been widely introduced into practice.

Cholangioscopy with direct visualization of the stricture area significantly increases the specificity and diagnostic accuracy of ERCP improving the effectiveness of biopsy, provided it is performed under cholangioscope control. In near future, with improvement in the performance characteristics of ultrathin endoscopes with the expansion of diagnostic capabilities through image magnification and narrow band interference will obviously lead to increased efficacy of the ERCP procedure supplemented by cholangioscopy.

Of the ERCP- associated techniques, probe CLE should be thought as the most promising. With an increase in the number of clinics with CLE devices, we should undoubtedly expect an increase in the number of publications on the effective use of endomicroscopy in the differential diagnostics of biliary strictures. However, the high cost of CLE sessions remains a powerful limiting factor in the development of the technique.

Besides analyzing the sensitivity, specificity and accuracy of the various examination techniques described above, a promising combination for effective differential diagnosis of biliary strictures in general and cholangiocarcinoma in particular, is an inexpensive "routine" ultrasound with EUS (with FNB, if possible) and subsequent ERCP with biopsy and sampling of cytological material. At the same time, when the above scheme is ineffective, it is reasonable to use all the diagnostic capabilities available in any particular clinic for the confident and correct diagnosing.

Bibliography

1. Glushkov NI., *et al*. "Minimally invasive surgery for gall stones in elderly patients". *Pirogov Russian Journal of Surgery* 10 (2010): 53-58.

2. Cha IH., *et al*. "Metastatic common bile duct cancer from pulmonary adenocarcinoma presenting as obstructive jaundice". *The Korean Journal of Gastroenterology* 61 (2013): 50-53.

3. Galperin EI and Dyuzheva TG. "Lectures on pancreatobiliary surgery". Edited by E.I. Galperin and T.G. Dyuzheva (2011).

4. Moreno Luna LE., *et al*. "Advanced cytologic techniques for the detection of malignant pancreatobiliary strictures". *Gastroenterology* 131 (2006): 1064-1072.

5. Taylor AC., *et al*. "Prospective blinded study of MRCP compared to ERCP and assessment of their respective clinical roles". *Gastroenterology* 118 (2000): A207.

6. Parsi MA. "Peroral cholangioscopy-assisted guidewire placement for removal of impacted stones in the cystic duct remnant". *World Journal of Gastroenterology* 1 (2009): 59-61.

7. Costamagna G., *et al*. "4633 Endoscopic sphincterotomy for common bile duct stones: long-term follow-up and risk analysis for recurrence". *Gastrointestinal Endoscopy* 51 (2000): AB189.

8. Weber A., *et al*. "Diagnostic approaches for cholangiocarcinoma". *World Journal of Gastroenterology* 14 (2008): 4131-4136.

9. Sharma MP., *et al*. "Aetiological spectrum of obstructive jaundice and diagnostic ability of ultrasonography: a clinician's perspective". *Tropical Gastroenterology* 20 (1999): 167-169.

10. Hye Cha., *et al*. "Metastatic Common Bile Duct Cancer from Pulmonary Adenocarcinoma Presenting as Obstructive Jaundice". *The Korean Journal of Gastroenterology* 61 (2013): 50-53.

11. Rösch T., *et al*. "A prospective comparison of the diagnostic accuracy of ERCP, MRCP, CT, and EUS in biliary strictures". *Gastrointestinal Endoscopy* 55 (2002): 870-876.

12. Yashina NI., *et al*. "Difficulties in the diagnosis of pancreatic head cancer in computer tomography". XXXIX Session of CRI (2013): 68.

13. Dumot JA., *et al*. "ERCP: current uses and less-invasive options". *Cleveland Clinic Journal of Medicine* 73 (2006): 418-425.

14. Shiryaev SV., *et al*. "The current state of PET diagnostics in oncology". Report at the Meeting of the Moscow Cancer Society (2009).

15. Anderson CD., *et al*. "Fluorodeoxyglucose PET imaging in the evaluation of gallbladder carcinoma and cholangiocarcinoma". *The Journal of Gastrointestinal Surgery* 8 (2004): 90-97.

16. Reinhardt MJ., *et al*. "Detection of Klatskin's tumor in extrahepatic bile duct strictures using delayed 18F-FDG PET/CT: preliminary results for 22 patient studies". *The Journal of Nuclear Medicine* 46 (2005): 1158-1163.

17. Itoi T., *et al*. "Diagnostic peroral video cholangioscopy is an accurate diagnostic tool for patients with bile duct lesions". *Clinical Gastroenterology and Hepatology* 8 (2010): 934-938.

18. Tischendorf JJ., *et al*. "Cholangioscopic characterization of dominant bile duct stenoses in patients with primary sclerosing cholangitis". *Endoscopy* 38 (2006): 665-669.

19. Da Silveria EB., *et al*. "An economic evaluation from randomized trial data comparing ERCP to MRCP in suspected biliary obstruction". *Gastrointestinal Endoscopy* 65 (2007): AB 95.

Volume 7 Issue 10 October 2020