ERCP on a Cohort of 2,986 Patients with Cholelithiasis: a 10-year Experience of a Single Center

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INTRODUCTION

The development of stone extraction techniques in recent years has enabled endoscopic treatment for the majority of cases presenting with suspected bile duct stones. The success rate for endoscopic stone extraction is high, many reports stating that at least 90% of stones are removed after conventional endoscopic sphincterotomy [1]. Occasionally, the management of bile duct stones can be difficult when faced with large and multiple stones or distal common bile duct (CBD) variants. The success of endoscopic retrograde cholangio-pancreatography (ERCP) may vary depending on anatomical factors such as the location of papilla adjacent to a diverticulum, the surgically modified anatomy after Billroth II resection and Roux-en-Y gastrojejunostomy, or if performed for postoperative biliary complications [2-4]. When selective biliary cannulation is difficult, an alternative to the standard technique such as precut papillotomy is required [5].

On the other hand, a good technique implies a selective cannulation of the CBD and the use of pancreatography only when necessary in order to avoid pancreatic complications due to the contrast agent. These issues are strongly related to the anatomical characteristics and the endoscopists’ experience.

An important aspect regarding the endoscopic treatment of cholelithiasis is the stone extraction in the elderly, as CBD...
stones occur more frequently with increasing age. In these patients, the incidence of the acquired duodenal diverticula is also increased [6, 7]. Biliary tract surgery carries an important risk of morbidity and mortality, therefore the endoscopic approach is a better alternative, but with the amendment that it is still invasive and more difficult to perform on the elderly.

ERCP may be a part of the diagnostic and therapeutic process and can also be of assistance in special conditions, such as the Mirizzi syndrome (extrinsic compression of the common hepatic duct by stones impacted in the cystic duct or gallbladder neck) [8].

Our aim was to evaluate the outcome of therapeutic ERCP performed for bile duct stones, with respect to the local anatomical characteristics that influence the success rate of cannulation and stone extraction. We also aimed to assess the factors that favour the opacification of the Wirsung duct in patients who have undergone pancreatography. Finally, we analyzed the anatomical characteristics that favour a recurrence of gallstones.

**METHODS**

A total of 3,097 consecutive ERCPs were performed in 2,986 patients at the endoscopic unit of the Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania during a 10-year period (2002-2011). The study refers only to patients with bile duct stones. Patients with bile duct stenoses or pancreatic diseases were excluded. The indication for ERCP was established in the presence of clinical and imaging signs of cholelithiasis. The clinical and imaging findings suggesting the CBD stone presence were biliary colic or abdominal pain and jaundice, plus acute pancreatitis or cholangitis. Until 2007, the diagnosis relied mainly on ultrasonography, while afterwards endoscopic ultrasonography and magnetic resonance cholangiopancreatography were used occasionally. The patient characteristics were analysed from the medical records and from the endoscopy department database. On the day of admission, every patient routinely underwent clinical examination, electrocardiogram, blood tests (complete blood cell count, liver, pancreas and renal function tests, clotting screen and electrolytes) and chest radiography. The biological tests were also assessed 24 and 48 hours after ERCP.

All ERCPs were performed by an experienced endoscopist, with a 7-year experience in ERCP before the start of the study. In the last 4 years of the study, two more physicians in training took part in performing ERCP, under the strict supervision of and finalized by the chief endoscopist. The procedures were performed with standard endoscopes (Olympus duodenoscope TGF-145) with an outer diameter of 12 mm and a working channel of 4.2 mm. Endoscopic sphincterotomy was performed in patients with bile duct enlargement, in those with clinical, ultrasonographic or radiological suspicion of gallstones and in patients with significant cholerasis.

Standard techniques were used for bile duct stone removal: Dormia basket or balloon extraction, or mechanical lithotripsy. Endoprostheses were used when appropriate for bile duct drainage. In patients with difficult stone extraction, precut papillotomy was performed. We did not use balloon dilatation in patients with large stones. Antibiotics were not routinely administered before the procedure, except in patients with valvular heart disease and in case of cholangitis. No bile samples for bacteriological evaluation were prelevated. The heart rate, electrocardiogram, blood pressure and peripheral oxygen saturation were continuously monitored. All patients received 2 L/min oxygen through a nasal cannula during the procedure. The endoscopic procedure was performed with the patient under conscious sedation with i.v. administered midazolam and in a few patients with propofol, without using orotracheal intubation. Butylscopolamine was administered for duodenal relaxation. Pharyngeal anesthesia was induced with a 10% lidocaine spray. The gastroenterologist performed the sedation, but when propofol administration was required, the anesthesiologist assisted for the entire procedure.

The data collected included patients’ age, sex, history of previous interventions / surgery, endoscopic and radiological findings, endoscopic interventions, cannulation success rate and success rate of stone extraction.

We divided the follow-up into two equal periods: 2002-2006 and 2007-2011, in order to analyse the results depending on the increasing experience of the operator. In addition, we analysed the anatomical particularities related with increasing age.

Because of the high risk of acute pancreatitis after ERCP and the role of pancreatography in this complication, we divided the study group depending on whether Wirsung duct opacification occurred and we also analysed the factors favouring opacification.

Finally, we analysed the factors associated with the success of endoscopic stone extraction, especially the anatomical features influencing the results. We defined endoscopic success as the complete removal of stones, regardless of the number of ERCP sessions required, and endoscopic failure as the inability to remove the stones. For diagnosing recurrent cholelithiasis, an asymptomatic period of six months had to follow after the first intervention. The anatomical factors associated with recurrent lithiasis were also analysed. We referred to CBD stones as “difficult” when their size was > 15 mm, when lithotripsy was necessary, in case of post-surgery variants or Mirizzi syndrome.

**Statistical analysis**

The data were analysed using descriptive statistics. The continuous variables were tested for normality of distribution using the Kolmogorov-Smirnov test. The values were presented as medians and percentiles (25th, 75th) for all continuous and as frequencies for categorical factors. Univariate analysis was used in order to find out the factors associated with the detection of CBD stones and the factors which influenced the success rate of stone extraction. The differences between groups were compared using the χ² test or the Fisher exact probability test, when appropriate. The Mann-Whitney U test was used for continuous variables. The variables that reached the p<0.2 criterion of significance in univariate analysis were included in the multivariate analysis in order to evaluate the independent factors associated with success rate. The level of statistical significance was set at p<0.05. We tested the area under the receiver operating characteristic curve (AUROC) in order to find the factors that could increase the probability of diagnosing the stones. The cut-off values for age and CBD
diameter were chosen for a maximum sum of sensitivity and specificity. All statistical analyses were performed with MedCalc Software, Mariakerke, Belgium, Version 12.4.0.0.

RESULTS

We included 2,986 patients in the study, who were examined by ERCP between 2002-2011 (Fig. 1). Of these, 1,818 (61.3%) were women and 1,150 (38.7%) men. The median age was 62 (52; 72) years. In 2,173 patients (73.2%), ECRP confirmed the presence of gallstones in the bile ducts. The cannulation of the CBD failed in 1.7% of these patients. The success rate for gallstone extraction was 97.16%. The demography, history and ERCP data are displayed in Table I.

Table I. Findings at ERCP in the study group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of subjects (%)</th>
</tr>
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<tbody>
<tr>
<td>Roux en Y loop</td>
<td>6 (0.2%)</td>
</tr>
<tr>
<td>Billroth II anastomosis</td>
<td>32 (1.1%)</td>
</tr>
<tr>
<td>Billroth I anastomosis</td>
<td>53 (1.8%)</td>
</tr>
<tr>
<td>Cholecdocho-duodenoanastomosis</td>
<td>39 (1.3%)</td>
</tr>
<tr>
<td>Sphinctermodized papilla</td>
<td>326 (11%)</td>
</tr>
<tr>
<td>Surgical sphincteroplasty</td>
<td>12 (0.4%)</td>
</tr>
<tr>
<td>Bulging papilla</td>
<td>215 (7.2%)</td>
</tr>
<tr>
<td>Infundibular fistula</td>
<td>68 (2.3%)</td>
</tr>
<tr>
<td>Impacted gallstone</td>
<td>169 (5.7%)</td>
</tr>
<tr>
<td>Peripapillary diverticulum</td>
<td>424 (14.3%)</td>
</tr>
<tr>
<td>Opacification of the Wirsung duct</td>
<td>866 (29.2%)</td>
</tr>
<tr>
<td>Pancreas divisum</td>
<td>26 (0.9%)</td>
</tr>
<tr>
<td>Successful cannulation</td>
<td>2918 (98.3%)</td>
</tr>
<tr>
<td>Stone in the CBD or intrahepatic ducts</td>
<td>2173 (73.2%)</td>
</tr>
<tr>
<td>Mirrizi syndrome</td>
<td>38 (1.2%)</td>
</tr>
<tr>
<td>ERCP success rate</td>
<td>2094 (97.6%)</td>
</tr>
</tbody>
</table>

Fig. 1. Number of patients examined by ERCP along the study period.

The number of gallstones was as follows: 1 stone in 1421 (47.9%) patients, 2 stones in 273 (9.2%) patients, and 3 or more stones in 1,494 (50.3%) patients and large stones (>15 mm) in 379 (12.7%) patients. The smallest CBD diameter was 2 mm, the largest 40 mm, median 12 (10; 14) mm.

The age of patients in the 2007-2011 study period (63 years) was significantly higher than in the first period, 2002-2006 (61 years) (p=0.004). The male patients were significantly older than the female patients (p<0.001). We found no significant difference in the gender ratio between the two periods (p=0.6).

For the threshold value of CBD size above which the probability of finding a stone increased, an AUC of 0.735 was calculated, with a cut-off value of 12 cm, 56% sensitivity (CI 95% 19-22.4; specificity 88.34 CI 95% 85.9-90.5), above which the probability to find a stone was higher (AUC=0.547; p<0.001).

For the threshold value of CBD size above which the probability of finding a stone increased, an AUC of 0.735 was found, with a cut-off value of 12 cm, 56% sensitivity (CI 95% 54.58.2) and 77.5 specificity (CI 95% 74.5-80.5).

The anatomical features influencing the probability of identifying bile duct stones on ERCP were studied. In univariate analysis, older age, the second time period, the presence of peripapillary diverticulum, the bulging papilla (by inflammation due to mechanical lesions induced by the stones) and the enlargement of the CBD were significantly associated with the presence of gallstones (p<0.001). In order to establish which of the studied parameters influenced independently the probability of discovering a stone on ERCP, we built a predictive model using binary logistic regression. The results showed that a patient examined between 2007-2011 had a 1.18-fold higher probability to have CBD stones, when compared to a patient examined between 2002-2006. In patients with bulging papilla, we found a 38% lower probability to have a stone in the bile ducts. The patients with a CBD larger than 12 mm had a 2-fold higher probability of biliary stones. We found no significant probability of having stones for patients with choledocho-duodenoanastomosis or duodenal diverticula.

Considering the risk of acute pancreatitis after ERCP, the parameters influencing the opacification of the Wirsung duct are displayed in Table II.

The number of gallstones was as follows: 1 stone in 1421 (47.9%) patients, 2 stones in 273 (9.2%) patients, and 3 or more stones in 1,494 (50.3%) patients and large stones (>15 mm) in 379 (12.7%) patients. The smallest CBD diameter was 2 mm, the largest 40 mm, median 12 (10; 14) mm.

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The number of cases where the Wirsung duct was opacified (368 vs 498) was significantly lower in the 2007-2011 period (p<0.001). In addition, the use of the precut papillotomy technique decreased significantly in the second part of the study (8.2% vs 1.9%, p<0.001). The precut sphincterotomy, required overall in 4.21% of cases, was significantly associated with the additional presence of an impacted stone (p<0.001), but did not correlate significantly with the other anatomical changes.

In the 2007-2011 period, a significantly higher number of diverticula was found as compared to the first period (262 vs 162) (p<0.001). The patients with diverticula were significantly older than those without (70 years vs 60 years) (p<0.001). We calculated an age cut-off value of 74 years (sensitivity 20.6% CI 95% 19-22.4; specificity 88.34 CI 95% 85.9-90.5), above which the probability to find a stone was higher (AUC=0.547; p<0.001).

For the threshold value of CBD size above which the probability of finding a stone increased, an AUC of 0.735 was found, with a cut-off value of 12 cm, 56% sensitivity (CI 95% 54.58.2) and 77.5 specificity (CI 95% 74.5-80.5).

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The evaluation of the parameters influencing Wirsung opacification was performed using a predictive model resulted from binary logistic regression (Table III). A patient examined between 2007-2011 had a 16.9% lower probability of experiencing opacification of the Wirsung, as compared to a patient examined between 2002-2006. Patients with a bulging papilla had a 27.5% lower probability of having opacification of the Wirsung duct than those without bulging papilla. The subjects with infundibular fistula had a 41.4% lower probability
of having opacification of the Wirsung duct. An impacted stone decreased the probability of having opacification by 28.5%. The patients with papillary diverticula had a 1.22-fold higher probability of opacification of the Wirsung duct. A CBD larger than 12 mm in diameter led to a 18.2% lower probability of Wirsung opacification. An important observation of the study is the 3.0% prevalence of pancreas divisum in 866 patients.

Of the 2,173 patients with biliary lithiasis, 38 subjects were excluded due to Mirrizzí syndrome. In 49 (2.3%) cases the stones could not be extracted. The univariate analysis of variables having a probable influence on stone extraction efficacy can be seen in Table IV. A peripapillary diverticulum, the number of stones, their size and the Billroth I gastrojejunoanastomosis were associated significantly with stone extraction failure in univariate analysis. We used the lithotripter for the fragmentation of large stones in 3.3% of cases, with a success rate of 93.8%.

We assessed the potential independent predictive role of various variables through binary logistic regression (Table V). In patients with previous surgical sphincteroplasty, the stone extraction was more difficult (OR=0.061). In addition, stone size and prior surgical interventions such as Billroth I anastomosis had a negative influence on stone extraction. The Roux en Y and Billroth II anastomosis did not influence the therapy success, but the number of patients included in the study having these anatomical alterations was very small.

In our study group, 92 patients (4.3%) had recurrent biliary stones. When studying the anatomical factors possibly favouring recurrence, we noticed a significant association of stone recurrence with choledocho-duodenoanastomosis (p=0.05), post-gastrectomy Billroth I anastomosis (p=0.02), a dilated infundibulum (p=0.04), peripapillary diverticulum (p=0.006) and with stone size (p=0.006). The variables correlating independently with recurrent lithiasis were stone size (p=0.002, OR=0.354), infundibulum dilation (p=0.04, OR=0.132) and the presence of a peripapillary diverticulum (p=0.004, OR=0.285).

### DISCUSSION

ERCP is a technically challenging procedure, with reported rates of unsuccessful cannulation varying between 3% and 10% in expert hands [9, 10]. This study presents the results of a large experience in ERCP from one single center in Romania, with respect to the detection of stones and the factors that may influence the therapeutical success.

In our study the cannulation was successful in 98% of cases, similarly to other studies [11]. Failure to gain access to the bile duct is a common problem, which can be the result of operator inexperience or various anatomical factors. The rate of unsuccessful cannulation has been observed in other reports in 4.3-5.1% of cases; it was usually caused by the deep location of the ampulla of Vater in a periampullary diverticula, by the deformations or strictures of the pylorus and duodenum, or by post gastrectomy anatomical changes [12, 13].

We found that detection of lithiasis was influenced by the patient’s age (above 74), operator experience, previous surgical sphincteroplasty and a CBD diameter >12mm. In other reports, the pathologic finding with the highest positive predictive value for the diagnosis of choledocholithiasis was the CBD enlarged above 8 mm (PPV 75%) [14].

Successful stone clearance was reported in 86-98% of attempts [15]. In our study the success rate was of 98%, which is among the highest reported rates.

Some studies report that stone size over 15 mm is the cause of “difficult calculi” requiring fragmentation or a larger opening [16]. In our patients, the stone size influenced the extraction success rate. We used the lithotripter for the fragmentation of large stones in 3.3% of cases with a success rate of 93.8%, similar to other reports [17,18]. In the case of unsuccessful
fragmentation, temporary insertion of prostheses into the biliary tract may contribute to the removal of deposits, as was performed in 1.2% of our patients. The prevalence of Mirizzi syndrome found in our study group was similar to that reported in other papers [19].

Although many studies have been published regarding the feasibility of endoscopic stone extraction, reports on the association between difficult biliary cannulation and postoperative anatomic factors have been scarce on the subject of precut papillotomy [1, 20-24]. Precut papillotomy is usually used for biliary obstruction in 8.5-10% of patients [20-23, 25]. We found that precut papillotomy was necessary in 4.21% of our cases, especially in patients having impacted stones. Precut papillotomy did not correlate with presence of other anatomical variants. We recorded, however, a decrease in the use of this procedure during the study period; only 1.9% of cases were treated with precut papillotomy in the second period of the study, probably because of the increasing experience of the endoscopist.

Difficult lithiasis is not only a matter of dimensions, but also of anatomical variability. Surgically altered anatomy such as Billroth II reconstruction after gastrectomy may further impair the endoscopic access to the papilla of Vater. A successful cannulation rate of about 66% was reported in these patients, when the scope reached the papilla of Vater via an afferent loop [26]. In our cohort, the extraction of stones in patients with Billroth II or Roux-en-Y reconstruction was not different when compared to patients with normal anatomy, but the study group was too small for a clear conclusion.

Some studies report little difference between the patients with Billroth I reconstruction and those with normal gastric anatomy [27]. We found a difficult biliary cannulation in patients with Billroth I reconstruction, this type of anatomic variant being an independent predictor of unsuccessful extraction of stones, maybe due to the straightened duodenum and to the loss of stability when the duodenoscope is in the straight or short position.

The presence of diverticula in patients undergoing ERCP is another anatomical cause that hinders stone extraction. The duodenal diverticula are found in about 10 to 15% of the patients [28], or 5-23% as reported by other studies [7]. In our cohort, 14.4% of the patients had periampullary diverticula. The association between the increased incidence of choledocholithiasis and periampullary diverticula makes ERCP a technically demanding procedure [29]. Successful cannulation in this special situation was achieved in up to 97% of the patients [4]. Some studies report the failure rate of endoscopic sphincterotomy to be higher in patients

<table>
<thead>
<tr>
<th>Table IV. Univariate analysis of the factors associated with stone extraction from the bile ducts</th>
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<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Age (median; percentile 25; 75) (years)</td>
</tr>
<tr>
<td>Males (number; %)</td>
</tr>
<tr>
<td>Females (number; %)</td>
</tr>
<tr>
<td>2002-2006 period (number; %)</td>
</tr>
<tr>
<td>2007-2011 period (number; %)</td>
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<tr>
<td>Surgical sphincteroplasty (number; %)</td>
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<td>Peripapillary diverticulum (number; %)</td>
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<tr>
<td>CBD (median; percentile 25, 75) (mm)</td>
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<tr>
<td>Billroth I (number, %)</td>
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</table>

Number of gallstones

| 1                                           | 1347 (64.5%)         | 41 (83.6%)         | 0.01**|
| 2                                           | 272 (13.0%)          | 1 (2.0%)           |       |
| 3 or more                                    | 467 (22.4%)          | 7 (14.3%)          |       |

Size of gallstones

| 1-4 mm                                       | 403 (19.3%)          | 18 (36.7%)         |       |
| 5-9 mm                                       | 678 (32.5%)          | 9 (18.3%)          |       |
| 10-14 mm                                     | 638 (30.6%)          | 10 (20.5%)         |       |
| >15 mm                                       | 367 (17.6%)          | 12 (24.5%)         |       |

* Mann-Whitney test; ** χ2 test; *** Fisher's Exact Test

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<thead>
<tr>
<th>Table V. Binary logistic regression for the probability of stone extraction</th>
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<tr>
<td>Lower</td>
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<tr>
<td>Surgical sphincteroplasty</td>
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<tr>
<td>Diverticulum</td>
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<tr>
<td>Stone size (5-9 mm)</td>
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<td>Billroth I</td>
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</table>
with periampullary diverticula than in those with normal anatomy (4.8% vs 2.0%; p<0.05) [30]. Other studies showed that the procedural complication and mortality rates after attempted sphincterotomy were unaltered by the presence of diverticula (5.2% vs 4% and 0.9% vs 0.7%, respectively) [31]. In our patients, the presence of diverticula did not influence significantly the success rate of CBD stone extraction in the multivariate analysis.

Several studies showed no relationship between advanced age or coexisting medical conditions and morbidity/mortality after ERCP [32-35], even if elderly patients had significantly more often a periampullary diverticulum or multiple common bile duct stones. In these patients, difficult cannulation was mainly caused by the deviation of the papilla as a result of a diverticulum [36]. Cocking et al [37] reported a success rate of 88% in CBD clearance in the elderly and a complication rate of 8%.

Recurrent bile duct stone formation is not uncommon following endoscopic sphincterotomy. Different authors suggest an incidence ranging from 4% to 24% [12,35,38]. Of our patients, 4.3% had recurrent lithiasis. The risk factors described previously for recurrent choledocholithiasis were the bile duct diameter (>15 mm) and the presence of a periampullary diverticulum [39, 40]. We found that the anatomic characteristics associated independently with recurrent lithiasis were the stone size, the dilated infundibulum and the presence of peripapillary diverticula.

The opacification of Wirsung duct was of special interest in our study. In 29% of our patients, opacification of the Wirsung duct during ERCP was recorded. The number of pancreatographies in our study is smaller than in other reports (47.8%) [12]. There are few studies that have analysed the factors associated with pancreatography. We found a bulging papilla, infundibular fistulas, impacted stones, papilla diverticula and the experience of the operator as independent associations with recurrent lithiasis were the stone size, the dilated infundibulum and the presence of peripapillary diverticula.

An important strength of our study is represented by the large number of patients coming from a single specialised center. To the best of our knowledge, this is the first study published on large series of patients with cholestasis from South-Eastern Europe and there are few studies published on this subject in the last ten years. The success rate for the extraction of CBD stones is among the highest reported in the literature. The prevalence of pancreas divisum is reported for the first time in Romania. We are, however, aware that the study has some limitations related to the lack of information regarding the body mass index of patients, the lipid profile and the drugs administered to the patients after ERCP, especially ursodeoxycholic acid, which could have influenced the rate of recurrent lithiasis.

CONCLUSION

The endoscopic treatment of choledocholithiasis is highly effective and is influenced in part by the operator experience. In experienced hands, the success rate is high even in case of anatomical variants and difficult calculi. The rate of pancreatography is also dependent on operator experience. As a consequence of opacification of the Wirsung duct, we observed a prevalence of 3% of pancreas divisum in our patients. The presence of large stones and of periampullary diverticula were the risk factors for recurrent lithiasis.

Conflicts of interest: No conflict to declare.

REFERENCES


