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Diagnosis of malignant biliary obstruction: pondering over the ERCP, MRCP and histology

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Abstract

Objective: To compare the diagnostic accuracy of endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance pancreatography (MRCP) and histological examination for malignant biliary obstruction.

Methods: This retrospective study included patients admitted for biliary obstruction caused by biliary tree malignancy that underwent ERCP, MRCP and histological examination. Data were collected from the medical records. The primary endpoints were the area under the receiver operating characteristic (AUROC) curve value, sensitivity, specificity and overall diagnostic accuracy of the three procedures in terms of a final diagnosis of obstructive biliary malignancy; and the agreement between ERCP, MRCP and histological examination with the final diagnosis.

Results: A total of 160 patients were included in the study (85 males, 53.1%; mean ± SD age, 69.31 ± 10.96 years). Considering the final diagnosis, the performance of MRCP, ERCP and

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histology in assessing biliary tumours produced AUROC values of 0.88 (95% confidence interval [CI] 0.75, 0.90), 0.94 (95% CI 0.85, 0.99) and 0.80 (95% CI 0.70, 0.82), respectively. ERCP presented higher sensitivity, overall diagnostic accuracy and agreement with the final diagnosis than MRCP and histological examination.

Conclusion: These current data suggest that invasive methods such as ERCP with biopsy remain more reliable than non-invasive methods.

Keywords

Endoscopic retrograde cholangiopancreatography, magnetic resonance pancreatography, histology, malignant biliary obstruction

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Introduction

Cancers of the biliary tract include cholangiocarcinoma (CCA), ampulla of Vater cancer and gallbladder cancer. All subtypes of biliary tract cancers are rare and difficult to diagnose.[1] The majority of biliary tumours causing biliary obstruction have a poor prognosis because they are usually diagnosed at an advanced stage and resectable in <20% of cases.[1] CCA and gallbladder cancer arise from the biliary epithelium and ampullary tumours arise from the ampullary complex, distal to the confluence of the common bile and pancreatic duct.[2] According to their anatomical origin, CCAs can be differentiated into intrahepatic CCA and extrahepatic CCA.[2] Intrahepatic CCAs account for 5–10% of all CCAs. [2] Extrahepatic CCAs are divided into perihilar CCAs (Klatskin tumours) that originate from above the cystic duct and are responsible for 60–70% of extrahepatic CCAs; and distal CCAs that originate from below the cystic duct.[2] Gallbladder cancer is the sixth most common gastrointestinal cancer and the most common biliary tract malignancy, accounting for 80–95% of biliary tract cancers.[3]

Most ampullary carcinomas are adenocarcinomas, with two main distinct histological sub-types based on their origin: (i) intestinal from the intestinal epithelium overlying the ampulla; and (ii) pancreato-biliary from the epithelium of the distal common bile duct and the distal pancreatic duct.[4] Ampullary adenocarcinomas arising from the pancreato-biliary tract have a worse outcome compared with those arising from the intestinal epithelium.[4]

The aim of this current study was to compare the diagnostic accuracy of endoscopic retrograde cholangiopancreatography (ERCP), histological examination and magnetic resonance pancreatography (MRCP) for malignant biliary obstruction, pondering the reliability of these diagnostic procedures.

Patients and methods

Study design

This retrospective study compared the diagnostic accuracy of ERCP, histological examination and MRCP in patients with biliary tree malignancy causing biliary obstruction identified at the Department of Gastroenterology, Emergency County Hospital Timisoara, Romania, which is an advanced regional research centre in

gastroenterology and hepatology in Romania. All patients gave their written informed consent for their data to be used in science research and for procedures to be undertaken. According to Romanian legislation, ethical committee approval is not required for retrospective studies. The study was conducted according to the Declaration of Helsinki. The reporting of this study conforms to STROBE guidelines.[5]

Study population

The medical records of consecutive patients with biliary tree malignancy causing biliary obstruction between January 2016 and December 2020 were reviewed. The inclusion criteria were as follows: (i) patients with biliary tree malignancy that caused biliary obstruction; (ii) patients that underwent ERCP. For batch homogeneity and a better discrimination of the prognostic factors, the exclusion criteria were as follows: (i) nonobstructive intrahepatic CCAs; (ii) choledocholithiasis; (iii) patients <18 years. The pathology records were reviewed to identify the histologically-confirmed patients. The radiology reports were reviewed to find those patients with a magnetic resonance imaging (MRI) examination and MRCP. Patients that did not have an MRI and MRCP and those without histology were excluded. Age, sex, number of hospitalization days, metastasis, septic shock, acute cholangitis condition, surgical interventions and death were also recorded.

Laboratory data

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, creatinine, gamma glutamyl-transaminase (GGT) and alkaline phosphatase (AP) levels were measured using routine methods.

Magnetic resonance cholangiography

Magnetic resonance pancreatography evaluated the extrahepatic and intrahepatic bile ducts using a 1.5 T General Electric MRI system (Optima MR450w; GE Medical Systems, Chalfont St Giles, UK). Masses, infiltration of the bile ducts or gallbladder anomalies were searched for on the MRCP images.

Endoscopic retrograde cholangiography

Endoscopic retrograde cholangiopancreatography was performed between 48 h and 72 h from admission with an Olympus TJF-145 Video Duodenoscope (Olympus Medical Systems, Tokyo, Japan). All procedures were undertaken while the patient was under sedation or general anaesthesia according to the anaesthesiologist indications. Diagnosis by ERCP was made according to stricture localization and endoscopic aspect of the ampulla (when the ampulla was tumour infiltrated).

Histological examination

During ERCP, intraductal specimens were obtained with a forceps passed into the bile duct after a sphincterotomy. Under fluoroscopic guidance, the forceps was advanced via the papilla to the biliary stricture, opened and then closed to grasp a specimen from the distal aspect of the stricture. For ampullary tumours, forceps biopsy sampling was used to obtain specimens. The samples were immersed in 10% neutral buffered formalin for a minimum 6 h and no longer than 24 h, processed and embedded in wax. Then 3–4 μm thick tissue sections were obtained and routine staining with haematoxylin and eosin was undertaken in all patients. The biopsies were analysed by two experienced pathologists specializing in gastrointestinal pathology.

Study endpoints

The primary endpoints of this study were the diagnostic accuracy of MRCP, ERCP and histological examination for the final diagnosis of obstructive biliary malignancy using the area under the receiver operating characteristic (AUROC) curve values, their sensitivities and specificities, along with the negative predictive values and positive predictive values; and the agreement of these diagnostic procedures with the final diagnosis. Secondary endpoints were to assesses the canulation rates of ERCP and the type of stent used for each procedure.

Statistical analyses

All statistical analyses were undertaken using the R statistical package (R version 4.0.5; R Foundation for Statistical Computing, Vienna, Austria) and MedCalc® software (version 19.2.0; MedCalc Software, Ostend, Belgium). Normality of continuous variable distribution was tested using the Kolmogorov–Smirnov test. The significance of the difference between groups was assessed using Student's *t*-test (mean values, normal populations), Mann–Whitney *U*-test (median values, for not normally distributed populations) and Pearson's χ^2-test or Fisher's exact test (proportions). The diagnostic performance of ERCP, MRCP and histological examination was assessed using the AUROC. For each diagnostic approach, the sensitivity, specificity and accuracy were calculated and the 95% confidence intervals were determined. Agreement between findings from MRCP, ERCP and histological examination was assessed employing the inter-rater agreement kappa (k) values (Cohen's kappa and Fleiss' kappa for two and multiple ratters, respectively). Univariate and multivariate analyses were undertaken to determine the factors involved in different types of biliary tumours. Factors that were evaluated included bilirubin, AST, ALT, GGT, AP, adenopathy, metastasis, sex and acute cholangitis. The statistical analysis was conducted at a 5% level of statistical significance and all reported probability values were two-tailed. A P-value <0.05 was considered statistically significant.

Results

This retrospective study enrolled 160 patients. Of these, 85 (53.1%) were males and 73 (45.6%) had acute cholangitis. The demographic and clinical characteristics are presented in Table 1. The mean ± SD age was 69.31 ± 10.96 years. There was a significant decrease in total bilirubin levels between hospital admission and discharge day (mean ± SD of 12.09 ± 7.90 mg/dl to 9.23 ± 6.24 mg/dl, $P = 0.0004$).

The majority of the malignant strictures were caused by extrahepatic CCA (88 of

Table 1. Demographic and clinical characteristics of patients ($n = 160$) with biliary tree malignancy causing biliary obstruction.

Characteristic	Study cohort n = 160
Age, years	69.31 ± 10.96
Male	85 (53.1%)
High levels of AST and ALT	155 (96.9%)
High levels of GGT and AP	157 (98.1%)
Acute cholangitis	73 (45.6%)
Septic shock at admission	22 (13.8%)
Total bilirubin, mg/dl	
At admission	12.09 ± 7.90
At discharge	9.23 ± 6.24
Adenopathy	42 (26.3%)
Hospitalization duration, days	8.17 ± 4.72
Metastasis	31 (19.4%)
Surgery during the same admission	16 (10.0%)
Death	14 (8.8%)

Data presented as mean ± SD or *n* of patients (%).
AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl transaminase; AP, alkaline phosphatase.

160; 55.0%), followed by ampullary tumours (39 of 160; 24.4%), intrahepatic CCA (10 of 160; 6.3%) and gallbladder tumours with main biliary duct invasion (10 of 160; 6.3%) (Table 2). The type of stricture could not be determined in 13 of 160 patients (8.1%).

Table 3 shows the diagnostic performance for the three diagnostic tests evaluated in this current study. All three diagnostic tests had good AUROC values, while the Fleiss' Kappa value confirmed a slight-to-fair agreement among the three tests. There was a significant agreement between ERCP and MRCP. The histological examination was in less agreement with both ERCP (rather low Kappa value, although significant) and MRCP (very low Kappa value, nonsignificant). ERCP was in more agreement with the final diagnosis compared with MRCP and histological examination. Figure 1 shows the three receiver operating characteristic curves compared with the diagonal reference line, which corresponds to a random binary classification. The good discriminatory ability of the three diagnostic tests can be observed.

At biopsy, 119 patients had adenocarcinomas and 41 were nonconclusive. From the 41 nonconclusive biopsies, 21 (51.2%) had superior imaging with a conclusive diagnosis and in the 20 patients with inconclusive superior imaging, ERCP established

Table 2. Final diagnosis of patients ($n = 160$) with biliary tree malignancy causing biliary obstruction.

Tumour type	Study cohort n = 160
Ampullary tumour	39 (24.4%)
Intrahepatic CCA	10 (6.3%)
Extrahepatic CCA	88 (55.0%)
Inconclusive	13 (8.1%)
Gallbladder tumour	10 (6.3%)

Data presented as *n* of patients (%).
CCA, cholangiocarcinoma.

Table 3. Diagnostic performance of the three diagnostic tests evaluated in this study of patients ($n = 160$) with biliary tree malignancy causing biliary obstruction: endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance pancreatography (MRCP) and histological examination.

	Diagnostic tests ($n = 160$)		
Measure	ERCP	MRCP	Histology
AUROC[a]	0.94 95% CI 0.85, 0.99	0.88 95% CI 0.75, 0.90	0.80 95% CI 0.70, 0.82
Sensitivity	98.0% (147/150)	87.3% (131/150)	72.0% (108/150)
Specificity	90.0% (9/10)	90.0% (9/10)	90.0% (9/10)
Overall accuracy	97.5% (156/160)	87.5% (140/160)	73.1% (117/160)
Fleiss' Kappa	Kappa = 0.173; z = 3.79, $P = 0.000152$		
Cohen's Kappa; ERCP and MRCP	Kappa = 0.441; z = 6.24, $P < 0.0001$		
Cohen's Kappa; ERCP and histology	Kappa = 0.223; z = 3.98, $P < 0.0001$		
Cohen's Kappa; MRCP and histology	Kappa = 0.0352; z = 0.48, $P = 0.631$		
Cohen's Kappa; ERCP and the final diagnosis	Kappa = 0.805; z = 10.2, $P < 0.0001$		
Cohen's Kappa; MRCP and the final diagnosis	Kappa = 0.420; z = 2.54, $P < 0.0001$		
Cohen's Kappa; histological examination and the final diagnosis	Kappa = 0.212; z = 7.84, $P < 0.0001$		

[a]Area under the receiver operating curve (AUROC) was considered as the main indicator of diagnostic ability.
CI, confidence interval.

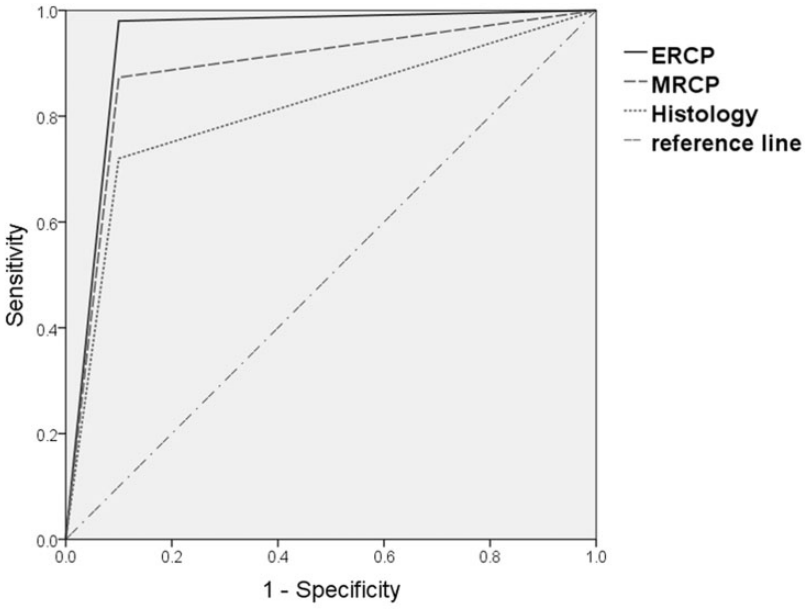

Figure 1. The receiver operating characteristic curve analysis for the three diagnostic tests analysed in patients ($n = 160$) with biliary tree malignancy causing biliary obstruction. All three tests show reliable diagnostic ability when compared with the reference line (i.e. corresponding to a random binary classification). ERCP, endoscopic retrograde cholangiopancreatography (ERCP); MRCP, magnetic resonance pancreatography (MRCP).

Table 4. Canulation rate at endoscopic retrograde cholangiopancreatography and type of stenting in patients ($n = 160$) with biliary tree malignancy causing biliary obstruction.

	n	Patients without cannulation	Canulation rate	Metal stent[a]	Plastic stent[a]
Total patient number	160	11	149 (93.1%)	99	42
Ampullary tumour	39	0	39 (100.0%)	25	6
Intrahepatic CCA	10	2	8 (80.0%)	6	2
Extrahepatic CCA	88	2	86 (97.7%)	68	18
Inconclusive tumours	13	7	6 (46.2%)	0	6
Gallbladder tumours	10	0	10 (100.0%)	0	10

Data presented as *n* of patients (%).

[a]Data for stent type based on patients that did not undergo surgery. The eight missing stents were due to the eight patients with ampullary tumours that went direct to surgery.

CCA, cholangiocarcinoma.

the final diagnosis in seven patients, with 13 patients remaining inconclusive.

The cannulation rate on ERCP was significantly different between lesions: 100.0% (39 of 39 patients) for ampullary tumours, 80.0% (eight of 10 patients) for intrahepatic CCA, 97.7% (86 of 88 patients) for extrahepatic cholangiocarcinoma (ECC), 46.2% (six of 13 patients) for inconclusive tumours and 100.0% (10 of 10 patients) for

Table 5. Univariate analyses of the predictive factors for each type of biliary tumour.

Factor	Tumour type.					
	Ampullary tumours	DCC	Klatskin tumours	ICC	Gallbladder tumours	Inconclusive tumours
High bilirubin	$P = 0.0001$	$P = 0.32$	$P = 0.008$	$P = 0.56$	$P = 0.98$	$P = 0.48$
High levels of AST and/or ALT	$P = 0.06$	$P = 0.27$	$P = 0.51$	$P = 0.20$	$P = 0.05$	$P = 0.35$
High levels of GGT and/or AP	$P = 0.4$	$P = 0.89$	$P = 0.96$	$P = 0.09$	$P = 0.08$	$P = 0.01$
Adenopathy	$P = 0.50$	$P = 0.02$	$P = 0.24$	$P = 0.01$	$P = 0.10$	$P = 0.004$
Male	$P = 0.80$	$P = 0.81$	$P = 0.09$	$P = 0.10$	$P = 0.03$	$P = 0.25$
Metastasis	$P = 0.02$	$P = 0.78$	$P = 0.10$	$P = 0.10$	$P = 0.0008$	$P = 0.01$
Acute cholangitis	$P = 0.48$	$P = 0.25$	$P = 0.35$	$P = 0.74$	$P = 0.04$	$P = 0.03$

DCC, distal cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl aminotransferase; AP, alkaline phosphatase.

gallbladder tumours (Table 4) ($P = 0.001$). In 11 patients, the ERCP procedure could not be undertaken for different reasons, including duodenal invasion and impossible canulation.

The results of the univariate analyses of the predictive factors for each type of biliary tumour are shown in Table 5. For ampullary tumours, high values of total bilirubin and metastasis ($P = 0.0001$ and $P = 0.02$, respectively) were significant predictive factors. For the other tumours, the significant predictive factors were as follows: for distal CCA, adenopathy ($P = 0.02$); for Klatskin tumours, high values of total bilirubin ($P = 0.008$); for gallbladder tumours, male sex, the presence of metastasis and acute cholangitis ($P = 0.03$, $P = 0.0008$ and $P = 0.04$, respectively); for inconclusive tumours, the presence of acute cholangitis, cholestasis (i.e. high levels of GGT and/or AP), metastasis and adenopathy ($P = 0.03$, $P = 0.01$, $P = 0.01$ and $P = 0.004$, respectively); and for ICC, adenopathy ($P = 0.01$).

The results of the multivariate analyses demonstrated the following: high bilirubin was an independent risk factor for ampullary tumours ($P = 0.01$); adenopathy for distal CCA ($P = 0.01$) and inconclusive tumours ($P = 0.001$); metastasis for ampullary tumours ($P = 0.04$) and gallbladder tumours ($P = 0.01$); and acute cholangitis was an independent risk factor associated with gallbladder cancer ($P = 0.01$) and inconclusive tumours ($P = 0.001$).

Discussion

It is very important to diagnose malignant obstructive jaundice in the early stages, but most patients are admitted to the hospital in advanced stages, with metastasis or vascular tumour invasion.[1] In the present study, 160 patients with malignant obstructive jaundice were included. Patients were also screened for choledocholithiasis according to The European Association for Endoscopic Surgery, since it is the most common cause of biliary obstruction.[6] The first-line imaging method in jaundiced patients is abdominal ultrasound since it can easily diagnose biliary obstruction. However, most biliary tumours are not easy to identify by abdominal ultrasound, so the next step is MRCP or endoscopic ultrasound (EUS) with fine needle aspiration. Although EUS is an effective method in assessing biliary stenosis, not all patients had been evaluated by this method so it was not included in the current study. Unfortunately, it was not possible to

evaluate all patients by EUS during the study period because the equipment was not available. MRCP was performed in all patients and had an overall accuracy of 87.5% (140/160), which was less than ERCP (97.5%; 156/160), but more than histology (73.1%; 117/160) for the diagnosis of biliary tumours. These findings were in contrast to two other published studies that showed an accuracy of 97% and 97.7% for MRCP.[7,8]For ERCP, the accuracy depends on the visualization of the bile duct's opacification with injected contrast agent. But since the duct's opacification depends on the canulation rate, this visualization may be limited in some patients. In this current study, in 11 of 160 patients the papilla could not be cannulated, so the bile ducts could not be visualized. In MRCP, the bile duct visualization is easier and it does not depend on the canulation rate like in ERCP. In this current study, the overall accuracy of ERCP was greater than that reported in a previous study (97.5% versus 67.7%).[9]

Magnetic resonance pancreatography has become the gold standard imaging method for the assessment of the biliary tree since it accurately visualizes ductal dilatations, strictures and intraluminal filling defects;[10] and it is superior to computed tomography.[11–14] However, it has some disadvantages: (i) it is contraindicated in patients with metallic implants and in patients that suffer from claustrophobia; and (ii) it is not widely available. ERCP is no longer a diagnostic tool as it was replaced by MRCP,[10] but all of this current cohort of patients needed endoscopic management, even if for only a short period of time in some patients (i.e. those that went to surgery). Unfortunately, most biliary malignancies are unresectable at diagnosis,[15] so only palliative endoscopic techniques can help them. ERCP is the first-line method that can decompress the biliary ducts with stent placement.[16] Another use of ERCP is for biopsy, which is an essential tool for diagnosis.[17]

In this current study, the sensitivity rate of histological examination was similar that reported in recent studies (60–70%).[15,18] From these 41 inconclusive lesions, 28 were diagnosed by either or both MRCP and ERCP. Nevertheless, after all imaging and histology investigations, the cause of biliary obstruction remained unknown in 13 patients. The best inter-test agreement was between ERCP and MRCP, with a Kappa value of 0.441. In contrast, the agreement of ERCP with the final diagnosis was significantly higher (Kappa value = 0.805).

All three diagnostic tests had the same specificity of 90%. The difference between the tests came from the sensitivity values, which entail different negative predictive values. These values are highly important for excluding the diagnosis, irrespective of the prevalence (important by itself).

Of the 160 patients included in the current study, the majority had extrahepatic CCAs (55.0%), while intrahepatic CCAs were found in 6.3% of patients. Univariate analyses identified factors that were associated with the tumours as follows: for ampullary tumours, high values of total bilirubin and metastasis; for distal CCA, adenopathy; for Klatskin tumours, high values of total bilirubin; for gallbladder tumours, male sex, the presence of metastasis and acute cholangitis; for inconclusive tumours, the presence of acute cholangitis, cholestasis, metastasis and adenopathy; and for ICC, the presence of adenopathy. In multivariate analyses, high bilirubin, adenopathy, metastasis and acute cholangitis were independent factors associated with biliary tumours, similar to what has been described in the literature.[19,20]

This current study had several limitations. First, as it was a retrospective study, the data regarding associated diseases were incomplete. Secondly, not all patients were

evaluated using EUS because the equipment was not available in our department. Thirdly, patients with non-obstructive biliary tumours were excluded from the study. Fourthly, on the basis that this was a hospital-based study and the patients that underwent ERCP, biopsy and MRCP were those that had been admitted from the Emergency Room, the prevalence data cannot be extrapolated to the general population. Finally, the current study did not calculate predictive values, but rather focused on the diagnostic ability of each procedure.

In conclusion, these current data showed that there was good agreement between ERCP, MRCP and histology for the diagnosis of malignant biliary obstruction. This current study reinforces the fact that invasive methods such as ERCP with biopsy would bring better reliability in diagnosing malignant obstructive jaundice, a high-risk emergency medical condition, compared with non-invasive methods.

Author contributions

The authors contributed as follows: conceptualization, I.R. and R.S.; methodology, I.R. R.L., R.S., A.P., I.S.; software, R.L., D.L.; validation, I.R., D.L., R.S., S.T., A.D.; formal analysis, R.L., D.L.; investigation, A.B., I.R., T.M., B. M., A.G.; data curation, A.B., T.M., M.D.; writing—original draft preparation, I.R., R.L., D.L., R.S.; writing—review and editing, I.R., A.P., R. S., A.G., I.S., A.D., D.L.; visualization, I.R., M. D.; supervision, R.S.; project administration, I. R., R.S. All authors have read and agreed to the published version of the manuscript.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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